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Practitioner's Docket No. 57204 (71970)

JC10 Rec'd PCT/PTO 15 MAR 2002

CHAPTER II

TRANSMITTAL LETTER TO THE UNITED STATES ELECTED OFFICE (EO/US) (ENTRY INTO U.S. NATIONAL PHASE UNDER CHAPTER II)

PCT/KR99/00561	17 September 1999	04 November 1999
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED

CASPASE INHIBITOR
TITLE OF INVENTION

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APPLICANTS

Box PCT
Assistant Commissioner for Patents
Washington D.C. 20231
ATTENTION: EO/US

NOTE: To avoid abandonment of the application, the applicant shall furnish to the USPTO, not later than 20 months from the priority date: (1) a copy of the international application, unless it has been previously communicated by the International Bureau or unless it was originally filed in the USPTO; and (2) the basic national fee (see 37 C.F.R. § 1.492(a)). The 30-month time limit may not be extended. 37 C.F.R. § 1.495.

WARNING: *Where the items are those which can be submitted to complete the entry of the international application into the national phase are subsequent to 30 months from the priority date the application is still considered to be in the international state and if mailing procedures are utilized to obtain a date the express mail procedure of 37 C.F.R. §1.10 must be used (since international application papers are not covered by an ordinary certificate of mailing - See 37 C.F.R. §1.8.*

NOTE: Documents and fees must be clearly identified as a submission to enter the national state under 35 USC 371 otherwise the submission will be considered as being made under 35 USC 111. 37 C.F.R. § 1.494(f).

CERTIFICATION UNDER 37 C.F.R. § 1.10*
*(Express Mail label number is **mandatory.**)*
(Express Mail certification is optional.)

I hereby certify that this paper, along with any document referred to, is being deposited with the United States Postal Service on this date March 15, 2002, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number **EL932681106US**, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Susan M Dillon
(type or print name of person mailing paper)

Susan M. Dillon
Signature of person mailing paper

WARNING: *Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.*

***WARNING:** Each paper or fee filed by "Express Mail" **must** have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).*
*"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will **not** be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.*

1. Applicant herewith submits to the United States Elected Office (EO/US) the following items under 35 U.S.C. 371:

   a. [X] This express request to immediately begin national examination procedures (35 U.S.C. 371(f)).

   b. [X] The U.S. National Fee (35 U.S.C. 371(c)(1)) and other fees (37 C.F.R. § 1.492) as indicated below:

2. Fees

CLAIMS FEE	(1) FOR	(2) NUMBER FILED	(3) NUMBER EXTRA	(4) RATE	(5) CALCULATIONS
[ ]*	TOTAL CLAIMS	16 - 20 =	0	x $ 18.00 =	$0
	INDEPENDENT CLAIMS	1 - 3 =	0	x $ 84.00 =	$0
	MULTIPLE DEPENDENT CLAIM(S) (if applicable) + $280.00				$280.00
BASIC FEE**	[ ] U.S. PTO WAS INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where an International preliminary examination fee as set forth in § 1.482 has been paid on the international application to the U.S. PTO: [ ] and the international preliminary examination report states that the criteria of novelty, inventive step (non-obviousness) and industrial activity, as defined in PCT Article 33(2) to (4) have been satisfied for all the claims presented in the application entering the national stage (37 CFR 1.492(a)(4)) ..... $100.00 [ ] and the above requirements are not met (37 CFR 1.492(a)(1)) ..... $710.00 [X] U.S. PTO WAS NOT INTERNATIONAL PRELIMINARY EXAMINATION AUTHORITY Where no international preliminary examination fee as set forth in § 1.482 has been paid to the USPTO, and payment of an international search fee as set forth in § 1.445(a)(2) to the U.S. PTO: [ ] has been paid (37 CFR 1.492(a)(2)) ..... $740.00 [X] has not been paid (37 CFR 1.492(a)(3)) ..... $1040.00 [ ] where a search report on the international application has been prepared by the European Patent Office or the Japanese Patent Office (37 CFR 1.492(a)(5)) $890.00				$1,040.00
	Total of above Calculations				= $1,320.00
SMALL ENTITY	Reduction by ½ for filing by small entity, if applicable. Affidavit must be filed. (note 37 CFR 1.9, 1.27, 1.28)				- $
	Subtotal				$1,320.00
	Total National Fee				$1,320.00
	Fee for recording the enclosed assignment document $40.00 (37 CFR 1.21(h)). (See Item 13 below). See attached "ASSIGNMENT COVER SHEET".				$40.00
TOTAL	Total Fees enclosed				$1,360.00

   i. [X] A check in the amount of $1,360.00 to cover the above fees is enclosed.

   ii. [ ] Please charge Account No. _____ in the amount of $ _____.
   A duplicate copy of this sheet is enclosed.

***WARNING:* *"To avoid abandonment of the application the applicant shall furnish to the United States Patent and Trademark Office not later than the expiration of 30 months from the priority date: * * * (2) the basic national fee (see § 1.492(a)). The 30-month time limit may not be extended." 37 C.F.R. § 1.495(b).*

WARNING: *If the translation of the international application and/or the oath or declaration have not been submitted by the applicant within thirty (30) months from the priority date, such requirements may be met within a time period set by the Office. 37 C.F.R. § 1.495(b)(2). The payment of the surcharge set forth in § 1.492(e) is required as a condition for accepting the oath or declaration later than thirty (30) months after the priority date. The payment of the processing fee set forth in § 1.492(f) is required for acceptance of an English translation later than thirty (30) months after the priority date. Failure to comply with these requirements will result in abandonment of the application. The provisions of § 1.136 apply to the period which is set. Notice of Jan. 3, 1993, 1147 O.G. 29 to 40.*

3. [X] A copy of the International application as filed (35 U.S.C. 371(c)(2)):

NOTE: *Section 1.495 (b) was amended to require that the basic national fee and a copy of the international application must be filed with the Office by 30 months from the priority date to avoid abandonment "The International Bureau normally provides the copy of the international application to the Office in accordance with PCT Article 20. At the same time, the International Bureau notifies applicant of the communication to the Office. In accordance with PCT Rule 47.1, that notice shall be accepted by all designated offices as conclusive evidence that the communication has duly taken place. Thus, if the applicant desires to enter the national stage, the applicant normally need only check to be sure the notice from the International Bureau has been received and then pay the basic national fee by 30 months from the priority date." Notice of Jan. 7, 1993, 1147 O.G. 29 to 40, at 35-36. See item 14c below.*

a. [ ] is transmitted herewith.
b. [ ] is not required, as the application was filed with the United States Receiving Office.
c. [X] has been transmitted
   i. [X] by the International Bureau.
   Date of mailing of the application (from form PCT/IB/308):
   ii. [ ] by applicant on _____.
   Date

4. [X] A translation of the International application into the English language (35 U.S.C. 371(c)(2)):
a. [ ] is transmitted herewith.
b. [X] is not required as the application was filed in English.
c. [ ] was previously transmitted by applicant on _____.
   Date
d. [ ] will follow.

5. [X] Amendments to the claims of the International application under PCT Article 19 (35 U.S.C. 371(c)(3)):

NOTE: *The Notice of January 7, 1993 points out that 37 C.F.R. § 1.495(a) was amended to clarify the existing and continuing practice that PCT Article 19 amendments must be submitted by 30 months from the priority date and this deadline may not be extended. The Notice further advises that: "The failure to do so will not result in loss of the subject matter of the PCT Article 19 amendments. Applicant may submit that subject matter in a preliminary amendment filed under section 1.121. In many cases, filing an amendment under section 1.121 is preferable since grammatical or idiomatic errors may be corrected." 1147 O.G. 29-40, at 36.*

a. [ ] are transmitted herewith.
b. [ ] have been transmitted
   i. [ ] by the International Bureau.
   Date of mailing of the amendment (from form PCT/IB/308): _____.

ii. [ ] by applicant on _____.
Date

c. [X] have not been transmitted as
i. [X] applicant chose not to make amendments under PCT Article 19.
Date of mailing of Search Report (from form PCT/ISA/210): 12/29/00
ii. [ ] the time limit for the submission of amendments has not yet expired. The amendments or a statement that amendments have not been made will be transmitted before the expiration of the time limit under PCT Rule 46.1.

6. [X] A translation of the amendments to the claims under PCT Article 19 (38 U.S.C. 371(c)(3)):
a. [ ] is transmitted herewith.
b. [ ] is not required as the amendments were made in the English language.
c. [X] has not been transmitted for reasons indicated at point 5(c) above.

7. [X] A copy of the international examination report (PCT/IPEA/409)
[X] is transmitted herewith.
[ ] is not required as the application was filed with the United States Receiving Office.

8. [X] Annex(es) to the international preliminary examination report
a. [X] is/are transmitted herewith.
b. [ ] is/are not required as the application was filed with the United States Receiving Office.

9. [ ] A translation of the annexes to the international preliminary examination report
a. [ ] is transmitted herewith.
b. [ ] is not required as the annexes are in the English language.

10. [X] An oath or declaration of the inventor (35 U.S.C. 371(c)(4)) complying with 35 U.S.C. 115
a. [ ] was previously submitted by applicant on _____.
Date
b. [X] is submitted herewith, and such oath or declaration
i. [X] is attached to the application.
ii. [ ] identifies the application and any amendments under PCT Article 19 that were transmitted as stated in points 3(b) or 3(c) and 5(b); and states that they were reviewed by the inventor as required by 37 C.F.R. 1.70.
iii. [X] will follow.

Other document(s) or information included:

11. [X] An International Search Report (PCT/ISA/210) or Declaration under PCT Article 17(2)(a):
a. [X] is transmitted herewith.
b. [ ] has been transmitted by the International Bureau.
Date of mailing (from form PCT/IB/308): _____.
c. [ ] is not required, as the application was searched by the United States International Searching Authority.
d. [ ] will be transmitted promptly upon request.

e. [ ] has been submitted by applicant on _____.
Date

12. [X] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98:
a. [ ] is transmitted herewith.
Also transmitted herewith is/are:
[ ] Form PTO-1449 (PTO/SB/08A and 08B).
[ ] Copies of citations listed.
b. [X] will be transmitted within THREE MONTHS of the date of submission of requirements under 35 U.S.C. 371(c).
c. [ ] was previously submitted by applicant on _____.
Date

13. [X] An assignment document is transmitted herewith for recording.

A separate [ ] "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or [X] FORM PTO 1595 is also attached.

_____
_____
_____

14. [X] Additional documents:
a. [X] Copy of request (PCT/RO/101)
b. [X] International Publication No. WO 01/21600
i. [X] Specification, claims and drawing
ii. [ ] Front page only
c. [ ] Preliminary amendment (37 C.F.R. § 1.121)
d. [X] Other

PCT/IB/306
PCT/IPEA/401
PCT/IPEA/402

15. [X] The above checked items are being transmitted
a. [X] before 30 months from any claimed priority date.
b. [ ] after 30 months.

16. [ ] Certain requirements under 35 U.S.C. 371 were previously submitted by the applicant on _____, namely:

_____
_____

AUTHORIZATION TO CHARGE ADDITIONAL FEES

WARNING: *Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges if extra claims are authorized.*

NOTE: "A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as

incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

NOTE: "Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

[X] The Commissioner is hereby authorized to charge the following additional fees that may be required by this paper and during the entire pendency of this application to Account No. **04-1105**.

[X] 37 C.F.R. 1.492(a)(1), (2), (3), and (4) (filing fees)

WARNING: *Because failure to pay the national fee within 30 months without extension (37 C.F.R. § 1.495(b)(2)) results in abandonment of the application, it would be best to always check the above box.*

[X] 37 C.F.R. 1.492(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.492(d)), it might be best not to authorize the PTO to charge additional claim fees, except possible when dealing with amendments after final action.

[X] 37 C.F.R. 1.17 (application processing fees)
[X] 37 C.F.R. 1.17(a)(1)-(5)(extension fees pursuant to § 1.136(a).
[ ] 37 C.F.R. 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. 1.28(b) requires "Notification of any change in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying . . . issue fee." From the wording of 37 C.F.R. § 1.28(b): (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

[ ] 37 C.F.R. § 1.492(e) and (f) (surcharge fees for filing the declaration and/or filing an English translation of an International Application later than 30 months after the priority date).

SIGNATURE OF PRACTITIONER

Reg. No.: 40,927

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10/088288
PCT/KR00/01047
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CASPASE INHIBITOR

Technical Field

The present invention relates to a novel isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof which can serve as an inhibitor for protein caspases (cysteinyl-aspartate proteinases), a process for preparing the same and the use of the derivative as an inhibitor for caspases. The present invention also relates to a pharmaceutical composition for preventing inflammation and apoptosis which comprises the isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof and the process for preparing the same. The isoxazoline derivative according to the present invention can effectively be used in treating diseases due to caspases, for example, the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.

Background Art

All organisms in nature undergo the life cycle consisting of development, differentiation, growth and death. Recently, an extensive research has been made to a mechanism involved in apoptosis which would play a key role in the control of the life cycle and the outbreak of diseases. It has been reported that apoptosis is occurred by a number of factors, but largely due to three kinds of cellular signal transport systems: the first of which is a signal transport system by the protein-protein interaction (See, Muzio M. et al., *Cell* 85, 817, 1996; Humke E. W. et al., *JBC* 273, 15702, 1998), the

second, an incorporation of cytochrome C into cytoplasm via mitochondria (See, Liu X. et al., *Cell* 86:147, 1996; Li P. et al., *Cell* 91, 479, 1997), and the third, a cellular signal transport pathway by the SAPK(Stress-activated protein kinases) activation of mitogen-activation protein kinase(MAPK) enzymes. All the pathways have been known to activate caspases cascade. As such caspases, about 10 kinds of isoenzymes in human and 14 kinds in mouse have been identified (see, Thornberry N. A. et al., *Science* 28, 1312 1998; Green D. R. *Science* 28, 1309, 1998; Ahmad M., et al., *Cancer Res.* 15, 5201 1998). The enzymes exist within the cells in the form of proenzyme which has no enzymatic activity and converted into an activated form if the cells are damaged or are exposed to a substance which leads to cellular necrosis. An activated enzyme has a heterodimer structure in which two polypeptides, i.e. larger subunits with the molecular weight of about 17-20 kDa, and smaller subunits with the molecular weight of about 10 kDa are bound together.

At present, caspases are classified into three (3) groups in view of the genetic identification analysis results and the biochemical characteristics: the first group is caspase-1, 4 and 5 which are responsible for the processing of cytokine activation, the second is caspase-3, 6 and 7 which carry out apoptosis and the third is caspase-8, 9 and 10 which are responsible for enzymatic activation in the upstream of signal transport system of apoptosis.

Among these caspases, Caspase-3 group and Caspase-8, 9, 10 etc. were recently reported to be related to apoptosis, and diseases (see, Thornberry N.A. et al., *Science*, 28, 1312, 1998).

According to the recent research results, caspases are commonly activated as apoptosis is initiated, even though there is a minor difference depending upon the tissues and cells. The activated caspases then activate intracellular CAD(Caspase-activated DNAse) which finally digests intranuclear DNA to result in cell death (Sakahira H., et al., *Nature* 1 96, 1998; Enari M et al., *Nature* 1 43, 1998). In addition, they promote apoptosis by decomposing substrate such as PARP (Poly-ADP ribose polymerase) which is necessary for the survival of cells.

Meantime, according to the recent disease-related researches, it was reported that the activity of Caspase-3 is increased in the brain of dementia patient which promotes the production of beta-amyloid peptide from beta-amyloid precursor protein that is considered to be a major cause of dementia, thereby accelerating the apoptosis of brain cells (see, Kuida K. et al., *Nature* 28, 368, 1996). Further, it was reported that activation of caspases can be the direct inducer of various diseases such as sepsis (see, Haendeler J. et al., *Shock* 6, 405, 1996; Lenhoff R.J. et al., 29, 563, 1999), rheumatoid arthritis (Firestein G.S. et al., *J. Clin. Invest* 96(3), 1631, 1995), cerebral stroke (see, Hill I.E. et al., *Brain Res.*10, 398, 1995), ALS disease (see, Alexianu M.E. et al., *J. Neurochem* 63, 2365, 1994), autoimmune isease (see, Rieux-Laucat F, et al., *Science* 2, 1347, (1995), diabetes mellitusd(see, Juntti-Berggren et al., *Science* 2, 86, 1993), hepatitis (Haendeler J. et al., *Shock* 6, 405, 1996), organ transplantation rejection reaction (Koglin J. et al., *Transplantation*, 27, 904, 1999; Bergese S.D. et al., *Transplantation* 27, 904, 1999), gastric ulcer (see, Slomiany B.L. et al., *J. Physiol. Pharmacol.* 96, 1631, 1995), and the like.

The researches on three dimensional structure of caspase-1 and caspase-3, catalytic mechanism of the enzyme and enzyme-substrate specificity (see,

Wilson, K.P et al., *Nature* 370, 270, 1994; Walker, N.P.C. et al., *Cell* 78, 343, 1994; *Nature Struc. Biol.* 3, 619, 1996) revealed that Caspase-1 group has a hydrolase-substrate specificity for the peptide sequence of (P4)-Val-X-Asp(P1) and Caspase-3 group has a hydrolase-substrate specificity for the sequence of (P4)Asp-X-X-Asp(P1).

Z-VAD-fluoromethyl ketone, and Z-DEVD-fluoromethyl ketone which mimics the above amino acid sequence have already been used in the researches on the inhibitors and were proven to have an inhibitory activity on apoptosis of hepatic cells by an activation of caspases (see, Rodriguez I. Et al., *J. Exp. Med.*, 184, 2067, 1996; Rouquet N. et al., *Curr Biol.* 1, 1192, 1996; Kunstle G. et al., *Immunol. Lett* 55, 5, 1997), and on the apoptosis of brain cells by cerebral ischemias. However, since such peptide derivatives are deficient in drug property for clinical application, they cannot be used as therapeutics.

Fulminant hepatic failure (FHF) is a clinical syndrome resulting from massive death of liver cells or sudden and severe impairment of liver function (See: Trey, C. et al., 1970, *Progress in liver disease*, Popper, H. and F. Schaffner, eds. Grune and stratton, New York, pp282-298). The causes of FHF are diverse: hepatitis virus infection, drugs and toxins, alcohol, ischemia, metabolic disorder, massive malignant infiltration, chronic autoimmune hepatitis, etc. However, these mechanisms are not completely clear. Since the prognosis of FHF is very poor while its progress is very rapid, it is not uncommon that a patient falls in lethal condition in 1-2 weeks from the onset of this syndrome (See, Sherlock, S. 1993, *Adv. Intern. Med.* 38: 245-267). Consequently, the overall mortality in most series is very high. However, the hepatic lesion is potentially reversible, and survivors usually recover completely.

Different therapeutic options that have been tried in FHF include antibiotics, diuretics, corticosteroids, blood transfusion, charcoal haemoperfusion, and plasmaphresis. However, none of these methods have been shown to be effective in controlled studies. In recent years, liver transplantation is generally accepted as the only therapeutic option to actually improve the prognosis of this syndrome. However, liver transplantation cannot be the perfect treatment for FHF because of immune complication, viral or bacterial infection, and graft availability. Thus, a potent therapeutic agent which can protect hepatic cells from massive death during the acute phase is critically desired.

Apoptosis is a type of cell death characterized by a series of distinct morphological and biochemical changes accomplished by specialized cellular machinery. Apoptosis is an essential process to remove excess, unwanted and harmful cells and maintain homeostasis, but inappropriate apoptosis is implicated in many human diseases such as neurodegenerative diseases, ischaemic damage, autoimmune disorders, several forms of cancer. Recently, it became clear that apoptosis of hepatocytes is a critical cause of hepatic injury in viral hepatitis and alcoholic hepatitis and acute hepatic failure in fulminant hepatitis. Many changes which occur in a cell that received apoptotic signal reflect complex biochemical events carried out by a family of cysteine proteases called caspases.

Caspases inactivate proteins that protect living cells from apoptosis, such as I^{CAD}/DFF45, an inhibitor of the nuclease responsible for DNA fragmentation, and Bcl-2. At the same time, caspases contribute to apoptosis not only by direct disassembly of cell structures, but also by reorganizing cell structures indirectly by cleaving several proteins involved

in cytoskeleton regulation. Since caspase activation is closely related to the initiating, propagating, and terminal event of most forms of apoptosis, this family of enzymes are attractive potential targets for the treatment of disorders resulted from excessive apoptosis or insufficient apoptosis.

Several kinds of caspase inhibitors have been identified. Four distinct classes of viral inhibitors have been described: CrmA, p35, a family of IAP (inhibitors of apoptosis), and the hepatitis B virus-encoded HBx protein (See, Gottlob, K. et al., 1998, *J. Biol. Chem.* 273: 33347-33353). However, these molecules are not suitable as the therapeutic agent. Peptide-based caspase inhibitor such as z-VAD-fmk, z-DEVD-fmk, and Ac-YVAD-cmk has widely been used for research use and this inhibitor showed apoptosis-blocking activity in cellular level (See: Sane, A. T. et al., 1998, Cancer Res. 58: 3066-3072), in rodent models of liver injury caused by Fas or by TNF_{α} (See: Kunstle, G. et al., 1997, *Immunol. Lett.* 55: 5-10) or ischemia after liver transplantation (See: Cursio, R. et al., 1999, *FASEB J.* 13: 253-261). Petak and colleagues showed that a bi-functional anticancer agent, BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) had caspase inhibiting activity and inhibited drug-induced apoptosis *in vitro* (See: Petak, I. et al., 1998, *Cancer Res.* 58: 614-618). Recently, cyclooxygenase-2 (COX-2) inhibitors are arousing interest as potential therapeutic agents of FHF (See, McCormick, P. A. et al., 1999, *Lancet* 353: 40-41). However, the efficacy of these materials has not been clinically verified yet.

In the meantime, development of new drugs depends primarily on the availability of suitable animal models relevant to human hepatitis or hepatocytic damage. It is therefore very important to adopt a suitable animal model relevant to human FHF to test efficacy of a candidate for

therapeutic agent. Two types of experimental hepatitis model were reported. One is hepatic injury induced by bacterial lipopolysaccharide together with D-galactosamine (See: Galanos, C. et al., 1979, *Proc. Natl. Acad. Sci.*, 76: 5939; Lehman, V. et al., 1987, *J. Exp. Med.* 165-657), and the other is a recently developed experimental model, Con A-induced hepatitis (See: Tiegs, G. et al., 1992, *J. Clin. Invest.* 90: 196-203; .Mizuhara, H. et al., 1994, *J. Exp. Med.* 179: 1529-1537). Con A-induced hepatitis model closely mimics human FHF in many respects, especially in the role of Fas in pathogenesis. Fas is abundantly expressed on the hepatocyte and FasL is expressed on activated T cells and functions as an effector of cytotoxic lymphocytes. Injection of agonistic monoclonal anti-Fas antibody into adult mice caused rapid hepatic failure, indicating that abnormally activated Fas-FasL system may play a role in human fulminant hepatitis which can be caused by the activation of immune system such as cytotoxic T cells. Accumulating data such as the involvement of specific CTLs in the pathogenesis of FHF, the sensitivity of primary hepatocytes to Fas-mediated apoptosis *in vitro*, and the overexpression of Fas in hepatocytes transformed with human hepatitis virus are consistent with this hypothesis. In recent studies, the activation of Fas-FasL system has been proved to play an important role in the liver cell injury by Con A-induced hepatitis (See: Tagawa, Y. et al., 1998, *Eur. J. Immunol.* 28: 4105-4113). FasL was induced in the liver shortly after the Con A injection was predominantly expressed on intrahepatic T cells. These results indicate thar Fas-FasL system is a critical element in the development of Con A-induced hepatitis. At the same time, the induction of Con A-hepatitis is associated with the production of various cytokines such as IL-2, TNF_{α} , IL-6, IL-4, and IL-10.

Disclosure of Invention

The present inventors have conducted an extensive research for many years in order to develop new therapeutics suitable for caspase inhibitor which has a unique structure over those known in the art. As a result, the inventors have surprisingly discovered a novel isoxazoline derivative of formula (I) which has a different structure over the known inhibitors and has an excellent inhibitory activity against various substrates for caspases, and have completed the present invention.

It is therefore an object of the present invention to provide a novel isoxazoline compound of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof which are useful as a caspase inhibitor.

Another object of the present invention is to provide a process for preparing the compound of formula (I).

Further object of the present invention is to provide a caspase inhibitor which comprises an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof.

Still other object of the present invention is to provide a pharmaceutical composition for inhibiting caspases activity which comprises as the active ingredient a therapeutically effective amount of the isoxazoline derivative of formula (I) and pharmaceutically acceptable carrier.

Still further object of the present invention is to provide a pharmaceutical composition for preventing inflammation and apoptosis which comprises the isoxazoline derivative, pharmaceutically acceptable salts, esters and

stereochemically isomeric forms thereof and the process for preparing the same.

Further objects and advantages of the invention will become apparent through reading the remainder of the specification.

The foregoing has outlined some of the more pertinent objects of the present invention. These objects should be construed to be merely illustrative of some of the more pertinent features of the invention. Many other beneficial results can be obtained by applying the disclosed invention in a different manner or by modifying the invention within the scope of the disclosure. Accordingly, other objects and a more thorough understanding of the invention may be found by referring to the detailed description of the preferred embodiment in addition to the scope of the invention defined by the claims.

Brief Description Of Drawings

Fig. 1 represents a graph showing inhibition activity of the compound of the invention against recombinant caspase-1, -2, -3, -4, -6, -7, -8 and -9.

Fig. 2 represents a graph showing caspase inhibition activities of the compound of the invention in rat hepatocytes in which apoptosis was derived by TNF_α and Actinomycin D treatment.

Fig. 3 represents a graph showing the effect of the compound of the invention on the prevention of apoptosis in rat hepatocytes in which apoptosis were derived by TNF_α and Actinomycin D treatment.

Fig. 4 represents a dose-dependent inhibitory activity of the compound of the invention against AST and ALT activities elevated by ConA *in vivo*, wherein the crossbars show the average of each group and p value was calculated by student's t-test.

Fig. 5 represents a dose-dependent inhibition activity against cytokines elevated by ConA *in vivo*, wherein the crossbars show the average of each group and p value was calculated by student's t-test.

Fig. 6 represents a photograph showing inhibition activities of the compound of the invention in apoptotic lesions and morphological, histological changes of hepatocytes in ConA-treated mouse liver.

Fig. 7 represents an electrophoresis image showing inhibition activities of the compound of the invention on PARP cleavage caused by ConA-induced apoptotic death of hepatocytes. Each lane is representative of 10 mice per group.

Fig. 8 is a graphical representation showing hepatic protection of the compound of the invention from IFN_{γ} and anti-Fas antibody-induced apoptosis.

Fig. 9 represents hepatic protection of the compound of the invention from anti-Fas antibody-induced apoptosis.

Fig. 10 is a graph showing inhibition activity of the compound of the invention against caspase-3-like activity in anti-Fas antibody-treated liver tissues.

Fig. 11 represents protection of mice by the compound of the invention from anti-Fas antibody-induced lethality.

Fig. 12 is a graphical representation showing the protection of mice liver by the compound of the invention from TNF_{α} -induced apoptosis.

Fig. 13 is a graphical representation showing that the compound of the invention inhibits caspase-3-like activity in TNF_{α} -treated liver.

Fig. 14 is a graphical representation showing that the compound of the invention protects mice from TNF_{α} -induced lethality.

Fig. 15 is a graphical representation showing that the compound of the invention inhibits TNF_{α} /Actinomycin D-induced caspase activation and apoptosis in primary cultured rat hepatocytes.

Fig. 16 is a graphical representation showing that the compound of the invention prevents hepatocyte apoptosis preinduced by TNF_{α} /Actinomycin D.

Fig. 17 is a graphical representation showing that the compound of the invention prevents TNF_{α} /DaIN-mediated mortality.

BEST MODE FOR CARRYING OUT THE INVENTION

In advance of illustrating the present invention in datail, some important terms are defined as follows:

a) Simple Alkyl Chain (hereinafter referred to as "SAC") is meant by a

carbohydrate having C_{1-8}, and contains a branched isomeric form.

b) Simple CycloAlkyl Chain (hereinafter referred to as "SCAC" is meant by a cyclic compound having C_{3-10}.

c) Aryl group (hereinafter referred to as "Ar") represents benzene [1:2,3,4,5,6], naphthalene[1,2:1,2,3,4,5,6,7,8,], pyridine [2,3,4:2,3,4,5,6], indole[1,2,3,4,5,6,7: 1,2,3,4,5,6,7], quinoline[2,3,4,5,6,7,8: 2,3,4,5,6,7,8], isoquinoline[1,3,4,5,6,7,8: 1,3,4,5,6,7,8], furan [2,3:2,3,4,5], thiophene[2,3:2,3,4,5], pyrole[1,2,3: 1,2,3,4,5], pyrimidine [2,4,5,6: 2,4,5,6], imidazole[1,2,4,5:1,2,4,5], benzofuran[2,3;2,3,4,5,6,7], etc. in which the former digits within the bracket represents a position where the corresponding aryl group is connected to the inhibitor according to the present invention and the latter digits after the colon represents a position where the substituent Y defined later can be attached.

d) Side chain of amino acids represents the side groups which are attached to the chiral carbon of 20 natural amino acids.

Frequently referred terms are abbreviated as follows:
N-chlorosuccinimide : NCS
N-methylmorporline : NMM
N,N-dimethyl formamide : DMF
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide: EDC
1-hydroxybenzotriazole hydrate : HOBt
Trifluoroacetic acid : TFA
t-butoxycarbonyl : Boc
benzyloxycarbonyl : Cbz
methyl : Me

ethyl : Et

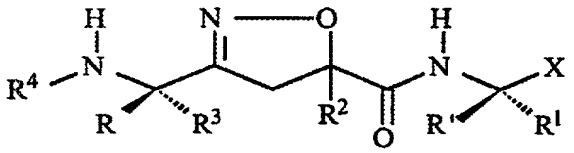
equivalent : Eq or eq

The term "stereochemically isomeric forms" as used in the foregoing and hereinafter defines all the possible isomeric forms which the derivative of formula (1) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes a mixture of all possible stereochemically isomeric forms, said mixture containing all diastereomers of the basic molecular structure. Stereochemically isomeric forms of the derivatives of the formula (1) are intended to be embraced within the scope of this invention.

The pharmaceutically acceptable salts as used in the foregoing and hereinafter comprises the therapeutically active non-toxic salt forms which can form the derivative of formula (1).

Hereinafter, the invention will be illustrated in more detail.

In one aspect, the present invention provides a novel isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof.



(I)

In the compound of formula (I), the substituents are defined as follows:
R and R' each independently represents hydrogen, simple alkyl chain

(-SAC), simple cycloalkyl (-SCAC), aromatic (-Ar), or simple alkyl chain substituted with aromatic (-SAC-Ar); preferably represents hydrogen. Throughout the description of the specification, R' has the same meaning as R unless specifically defined.

R^1 represents -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC); preferably represents $-CH_2COOH$.

R^3 represents -SAC, -SCAC, -Ar, -SAC-Ar, or side chain of amino acids; preferably represents $-CH(CH_3)_2$, $-CH_2COOH$, $-(CH_2)_2CO_2H$, $-CH_2C(=O)NH_2$ or $-(CH_2)_2C(=O)NH_2$.

In a case where an adjacent position of R^1 or R^3 become a stereogenic center, both the stereoisomeric compounds are intended to be embraced within the scope of the present invention. Similarly, a case where two forms of compounds are co-exist (a mixture of diastereomeric compounds) is embraced within the scope of the invention. In addition, the cases where R^1 or R^3 are composed of carboxylic acids or bases with side chain residue of amino acids, their protected forms such as simple esters or pharmaceutically acceptable salt forms are also embraced within the scope of the compounds according to the invention.

R^2 represents -H, -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), or $-(CH_2)_nOC(=O)R^6$ (in which R^6 = -SAC, -SCAC, -Ar, or -SAC-Ar; and n=1 or 2). Preferable R^2 represents $(CH_2)_n(O)_mAr'$ (in which n=0, 1, or 2; and m = 0 or 1; Ar' = substituted phenyl or imidazole), methyl or hydrogen.

In a case where an adjacent position due to R^2 become a stereogenic center, both the stereoisomeric compounds are embraced within the context of the compounds of the present invention, Similarly, a case where two forms of compounds are co-exist (a mixture of diastereomeric compounds) is embraced within the category of the compounds according to the invention. In addition, the cases where R^2 are composed of carboxylic acids or bases with side chain residue of amino acid, their protected forms such as simple esters or pharmaceutically acceptable salt forms are also embraced within the scope of the compounds according to the invention.

R^4 represents

a) amino acid residue in which ① the carboxyl group attached to the chiral carbon of amino acid is bound to the amine group to form an amide bond, ② the chiral carbon of amino acid has either R or S configuration, ③ the amino group attached to the chiral carbon of amino acid is protected by formyl, acetyl, propyl, cyclopropylcarbonyl, butyl, methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl or cyclopropylaminocarbonyl, or the amino group may be replaced with a hydrogen atom, and ④ the carboxyl group in the side chain may form an ester group with -SAC or -SCAC,

b) $-C(=O)R^7$ (in which R^7 = -SAC, -SCAC, -Ar, -SAC-Ar), $-CO_2R^8$ (in which R^8 = hydrogen or R^7), $-C(=O)NR^8R^8$, $-SOR^7$, $-SO_2R^7$, or -C(=O)CH=CH-Ar,

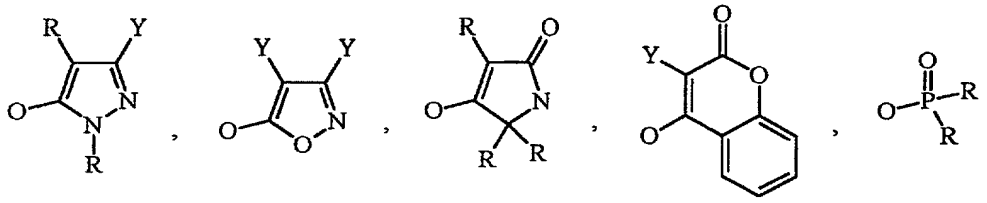
c) $-(C=O)-L-CO_2R^8$, in which L represents a divalent (=capable of double substitution) linker selected from a group consisting of C_{1-6} alkyl,

C_{3-8} cycloalkyl, furan, thiophene, diazole (1,2 or 1,3), triazole (1,2,3 or 1,3,4), tetrazole, oxazole, isoxazole, thiazole, isothiazole, diazine (1,2 or 1,3 or 1,4), triazine, -Ph(-R^9)- (in which R^9 = H, F, Cl, Br, I, CHO, OH, OCH_3, CF_3, OCF_3, CN, C(=O)Me), tetrahydrofuran, tetrahydrothiophene, 1,4-dioxane, -CH=C(R^{10})- (in which R^{10}=H, methyl, ethyl), -CH=CHCH(R^{10})- , -CH(OR^{10})CH_2-, -CH_2C(=O)CH_2-, -C(=O)CH_2CH_2-

In cases where R^1 and the adjacent R', and/or R^3 and the adjacent R are connected to each other to form a cyclic compound, R^1-R' or R^3-R together represents -$(CH_2)_n$-, -$(CH_2)_n$-O-$(CH_2)_m$-, or -$(CH_2)_n$-NR^{13}-$(CH_2)_m$- (in which n+m<9, R^{13}=-SAC, -SCAC, -Ar, -SAC-Ar, -C(=O)-SAC, -C(=O)-SCAC, -C(=O)-Ar, or -C(=O)-SAC-Ar);

X represents -CN, -CHO, -C(=O)R^{14} (in which R^{14} = -SAC, -SCAC, -Ar, -SAC-Ar, or -CHN_2), -C(=O)OR^{15} (in which R^{15} = -SAC, -SCAC, -Ar, or -SAC-Ar), -$CONR^{16}R^{17}$ (in which R^{16} and R^{17} each represents -H, -SAC, -O-SAC, -SCAC, -Ar, or -SAC-Ar), -C(=O)CH_2O(C=O)Ar" (in which Ar" = 2,6-disubstituted phenyl with F, Cl, Br, I, or CH_3), -C(=O)CH_2OR^{18} (in which R^{18} represents -SAC, -SCAC, -Ar, or -SAC-Ar), or -C(=O)CH_2OC(=O)R^{19} (in which R^{19} = -SAC, -SCAC, -Ar, or -SAC-Ar), or

X represents -$COCH_2$-W, wherein W represents -N_2, -F, -Cl, -Br, -I, -$NR^{20}R^{21}$ or -SR^{22} (in which wherein R^{20}, R^{21} and R^{22} each independently represents -SAC, -SCAC, -Ar, or -SAC-Ar or R^{20} and R^{21} are connected to form a cyclic compound); or W represents



in which Y represents -OH, OR^{23} (in which R^{23} = -SAC, or -SCAC), $-C(=O)R^{24}$ (in which R^{24} = -H, -SAC, or -SCAC), -F, -Cl, -Br, -I, -CN, -NC, $-N_3$, $-CO_2H$, $-CF_3$, $-CO_2R^{25}$ (in which R^{25} = -SAC, or -SCAC), $-C(=O)NHR^{26}$ (in which R^{26} = -SAC, or -SCAC), and $-C(=O)NR^{27}R^{28}$ (in which R^{27}, R^{28} = -SAC, or -SCAC) and can be mono- or poly-substituted at its maximum regardless of the order and the kinds.

Among the compound of formula (I), preferred are those in which R^4 represents $-C(=O)(CH_2)_pCOOZ$ (in which p is 1 to 4, and Z is hydrogen, -SAC, -Ar or -SCAC). Also preferred are those in which R^1 represents $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC).

Among the compound of formula (I), more preferred are those in which

a) R and R' represent hydrogen,

b) R^1 represents $-CH_2COOH$, $-CH_2COOCH_3$, or $CH_2COOCH_2CH_3$,

c) R^2 represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), SAC, Ar, or Hydrogen,

d) R^3 represents $-CH(CH_3)_2$, $-CH_2COOH$, $-(CH_2)_2CO_2H$, $-CH_2C(O)NH_2$ or $-(CH_2)_2C(O)NH_2$,

e) R^4 represents $-C(=O)(O)_nR^{29}$ (in which n=0, 1; R^{29}= -Ar or -SAC-Ar), $-SO_2R^{30}$ (in which R^{30}= -Ar or -SAC-Ar), or $-C(=O)NHR^{31}$ (in which R^{31} = -Ar, or -SAC-Ar), or

f) X represents $-C(=O)CHN_2$, $-C(=O)CH_2Br$, $-C(=O)CH_2Cl$, $-C(=O)CH_2OPh$

or -C(=O)CH_2OC(=O)Ar" (in which Ar"=2,6-dichlorophenyl, 2,6-difluorophenyl or 2,6-dimethylphenyl).

Most preferred compounds are selected from the group consisting of the following:

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid;

(2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 1-(N-methyl-N-methoxy)-amide;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid(LP and MP);

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid(LP and MP);

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid(LP and MP);

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-sulfonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(2S)-2-acetylamino-succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-

isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (diasteromeric mixture);
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid

(diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-

pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-

imidazolyl-methyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidinyl)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-4-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-difluorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)- pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dimethylbenzoyloxy)-pentanoic acid[diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-8-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-piperidine)-pentanoic acid[diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-pyrrolidine)-pentanoic acid

[diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-hydroxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(glutaroylamino)-propyl]-5-methyl-4,5-dihydro-iso-xazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid; and
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid methyl ester.

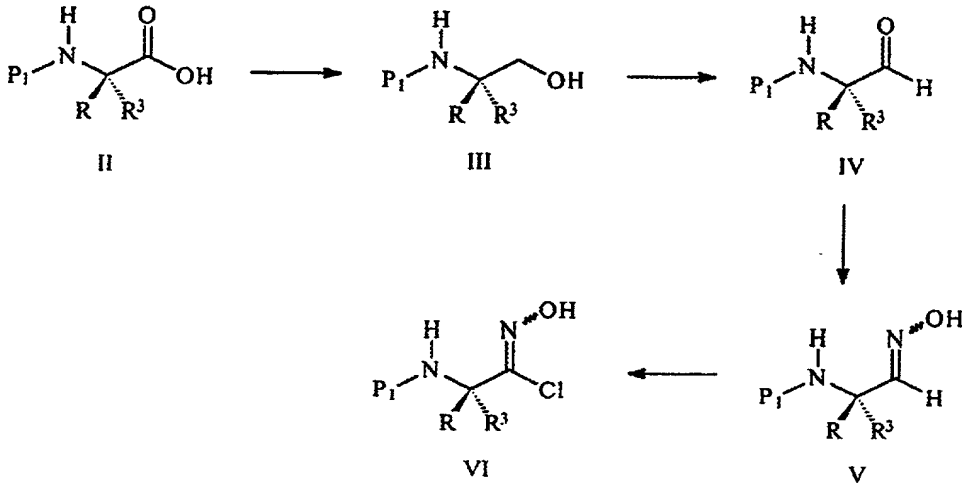
In another aspect, the present invention provides a process for preparing a compound of formula (I).

Hereinafter, a process for preparing the isoxazoline derivatives of formula (I) according to the present invention will be explained with respect to Reaction Schemes 1 and 2. It should be understood that the reaction schemes generally illustrate the specific process used in the present invention, but any modification of the unit operations may be made without departure of the spirit of the invention. Therefore, the present invention should not be limited to the following preferred embodiments.

In the first step, amino protected amino acid (II) (commerically available from Novabiochem) is reduced to give N-protected amino alcohol (III) which is then oxidized to give N-protected amino aldehyde (IV).

N-protected amino aldehyde (IV) is reacted with hydroxylamine-hydrochloride and sodium carbonate in a mixed solution of an alcohol and water to give an oxime (V) (syn- and anti-oxime). The resulting oxime derivative (V) is treated with NCS (N-chlorosuccinimide) in an aqueous solution of dimethylformamide to give hydroxamoyl chloride (VI). As the representative substituents used in the synthesis of hydroxamoyl chloride, the following groups may be exemplified: P_1 represents Cbz, t-Boc, Fmoc, Teoc(trimethylsilyl-ethyloxycarbonyl), etc.; R represents H and R^3 represents $-CH_2CH_2CO_2Bu(t)$, $-CH_2CO_2Me$, $-CH_2CO_2Bu(t)$, -isopropyl, phenylmethyl, and the like.

Reaction Scheme 1



In the above Reaction Scheme 1, the following combinations of a) to g) for the commercially available compounds (II) to (VI) may be synthesized.

a) P_1 = Cbz, R = H, R^3 = i-Pr

b) P_1 = t-Boc, R = H, R^3 = i-Pr

c) P_1 = Fmoc, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$

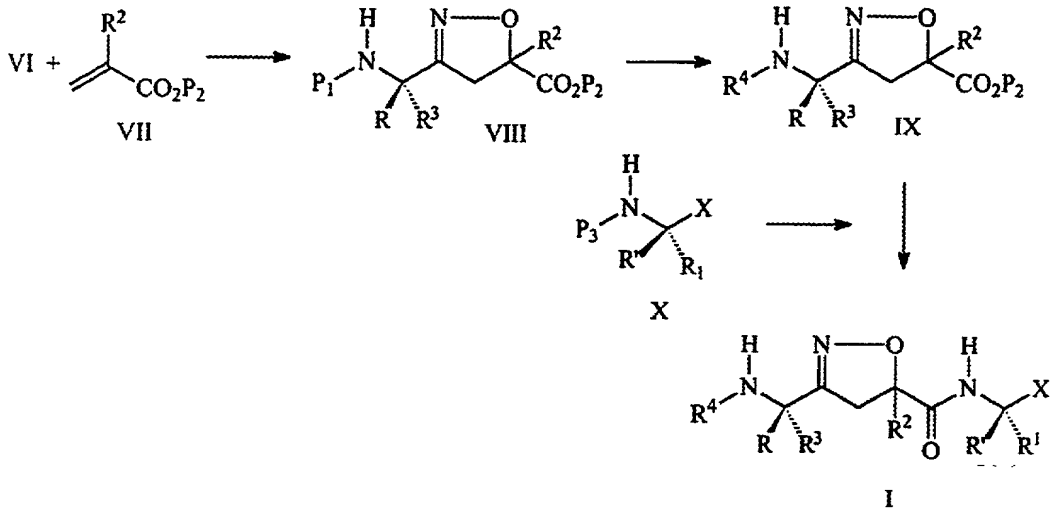
d) P_1 = t-Boc, R = H, R^3 = CH_2CO_2Me

e) P_1 = Cbz, R = H, R^3 = $CH_2CO_2Bu(t)$

f) P_1 = Fmoc, R = H, R^3 = $CH_2CO_2Bu(t)$

g) P_1 = Boc or Cbz, R = H, R^3 = CH_2Ph

Reaction Scheme 2



In the second step, the hydroxamoyl chloride (VI) thus obtained is then reacted with acrylate derivative (VII) to give isoxazoline derivative (VIII). If necessary, isoxazoline derivative (VIII) may be synthesized directly from the oxime derivative (V).

If a compound having the protecting group P_1 can be used as the inhibitor (for example, P_1 is a Cbz group), the isoxazoline derivative (VIII) is directly reacted with the compound (X) to give a compound of formula (I), and there is need to convert the protecting group P_1 into other substituent, P_1 is removed and R^4 is introduced thereinto.

In the above Reacion Scheme 2, the following combination of substituents may be synthesized.

In the compound (VIII),

a) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

b) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

c) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

d) P_1 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

e) P_1 = Fmoc, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = CH_3(or Et)

f) P_1 = Teoc, R = H, R^3 = i-Pr, R^2 = CH_3, P_2 = H

g) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2= $PhCH_2$, P_2=Et

h) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = Et

i) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = 1-naphthyl, P_2 = Et

j) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = 2-naphthyl, P_2 = Et

k) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = phenyl, P_2 = Et

l) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = 4-bromophenyl, P_2 = Et

m) P_1 = t-Boc, R = H, R^3 = i-Pr, R^2 = $AcOCH_2$, P_2 = Et

In the compound (IX),

a) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

b) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

c) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

d) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

e) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

f) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

g) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = Et

h) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = CH_2OPh, P_2 = H

i) R^4 = 2-naphthoyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = CH_3

j) R^4 = 2-naphthoyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = H

k) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

l) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

m) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = Et

n) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = H

o) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = Et

p) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, P_2 = H

q) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

r) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

s) R^4 = hydrocinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

t) R^4 = hydrocinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

u) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

v) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

w) R^4 = 1-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

x) R^4 = 1-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

y) R^4 = 3-indoleacetyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

z) R^4 = 3-indoleacetyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

aa) R^4 = 3-indolepropionyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

ab) R^4 = 3-indolepropionyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ac) R^4 = *trans*-cinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

ad) R^4 = *trans*-cinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ae) R^4 = phenylmethylsulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

af) R^4 = phenylmethylsulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ag) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = Et

ah) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, P_2 = H

ai) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = Et

aj) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, P_2 = H

ak) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = 1-imidazolyl, P_2 = Et

al) R^4 = 1-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = 1-imidazolyl, P_2 = H

am) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = CH_3

an) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, P_2 = H

ao) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = i-Pr, R^2 = CH_3, P_2 = CH_3

ap) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = i-Pr, R^2 = CH_3, P_2 = H

In the compound (X),

a) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =CO_2Me

b) P_3 = HCl+H, R = H, R^1=$CH_2CO_2Bu(t)$, X =CO_2Me

c) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$COCH_2N_2$

d) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$COCH_2Br$

e) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$COCH_2OPh$

f) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2OPh$

g) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2OPh$

h) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$,

X = $CH(OH)CH_2OC(O)Ph$(2,6-dichloro)

i) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$,

X =$CH(OH)CH_2OC(O)Ph$(2,6-dichloro)

j) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =CONMe(OMe)

k) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$, X =CONMe(OMe)

l) P_3 = Cbz, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2O$- (1-naphthyl)

m) P_3 = H, R = H, R^1=$CH_2CO_2Bu(t)$, X =$CH(OH)CH_2O$- (1-naphthyl)

In the compound (I),

a) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = CO_2H

b) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N_2$

c) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2Br$

d) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

e) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph$ (2,6-dichloro)

f) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = 2-naphthyloxymethylcarbonyl

g) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = 1-naphthyloxymethylcarbonyl

h) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

i) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

j) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

k) R^4 = 2-naphthalenesulfonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

l) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

m) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

n) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N_2$

o) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2Br$

p) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

q) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)$-Ph-(2,6-dichloro)

r) R^4 = N-acetyl-β -t-butyl aspartyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $CH(OH)CH_2OPh$

s) R^4 = N-acetyl-β -t-butyl aspartyl, R = H, R^3 = $CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

t) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X =

C(=O)NMe(OMe)

u) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_3$

v) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = CO_2CH_3

w) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = CO_2H

10x) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N_2$

y) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2Br$

z) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)$-Ph-2,6-dichloro

aa) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = C(=O)NMe(OMe)

ab) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = $PhOCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_3$

ac) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = CO_2CH_3

ad) R^4 = Cbz, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ae) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

af) R^4 = hydrocinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ag) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ah) R^4 = 1-naphthalenesulphonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ai) R^4 = 3-indoleacetyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

aj) R^4 = 3-indolepropionyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ak) R^4 = *trans*-cinnamoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

al) R^4 = phenylmethylsulfonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

am) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

an) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

ao) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OC(=O)Ph(2,6\text{-dichloro})$

ap) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

aq) R^4 = 2-quinolinecarbonyl, R = H, R^3 = i-Pr, R^2 = 1-imidazolyl, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OCPh$

ar) R^4 = 2-naphthoyl, R = H, R^3 = i-Pr, R^2 = H, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_3$

as) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = $(CH_2CH_2CO_2Bu(t)$, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

at) R^4 = $COCH_2CH_2CO_2Bu(t)$, R = H, R^3 = i-Pr, R^2 = CH_3, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2OPh$

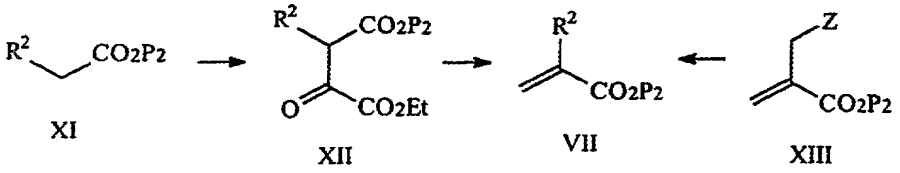
au) R^4 = 1-naphthoyl, R = H, R^3 = i-Pr, R^2 = $PhCH_2$, R^1 = $CH_2CO_2Bu(t)$, X = $C(=O)CH_2N(CH_2)_5$

In Reaction Scheme 2, the functional group X of compound (X) may be introduced by several unit operations after the reactions involved in the

synthesis of the compound (VIII) or (IX), or the compound (VIII) or (IX) already having desired substituent X may be proceed with the subsequent reactions.

The acrylate derivative (VII) may be synthesized by any one of two processes as depicted in Reaction Scheme 3 below.

Reaction Scheme 3



Ester derivative (XI) is reacted with diethyl oxalate to give oxalate derivative (XII) which is then reacted in the presence of a base to give desired acrylate derivative (VII). Alternatively, it may be synthesized by various processes starting from the known compound (XIII). That is, the known compound (XIIIa) is easily converted into compounds (XIIIb), (VIIe), (VIIf), (VIIg), etc.

In the compounds (XI) and (XII), the substituents are examplified as follows:

a) P_2 = Et, R^2 = Ph

b) P_2 = Et, R^2 = 4-bromophenyl

c) P_2 = Et, R^2 = 1-naphthyl

d) P_2 = Et, R^2 = 2-naphthyl

In the compounds (VII) and (XIII), the following combination of the substituents can be synthesized by the above process.

In the compound of (VII),

a) R^2 = Ph, P_2 = Et

b) R^2 = 4-bromophenyl, P_2 = Et

c) R^2 = 1-naphthyl, P_2 = Et

d) R^2 = 2-naphthyl, P_2 = Et

e) R^2 = CH_2OAc, P_2 = Et

f) R^2 = CH_2Ph, P_2 = Et

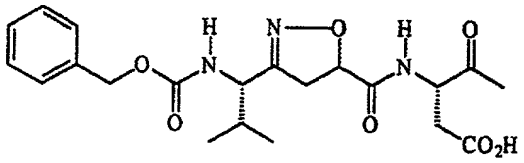
g) R^2 = CH_2OPh, P_2 = Et

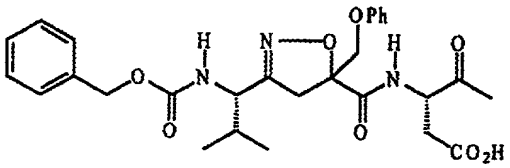
In the compound (XIII),

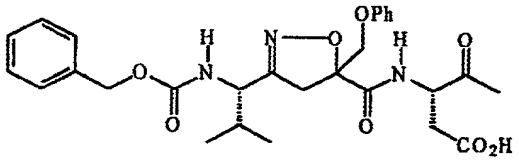
a) R^2 = Et, Z = OH

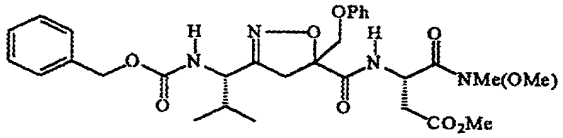
b) R^2 = Et, Z = Br

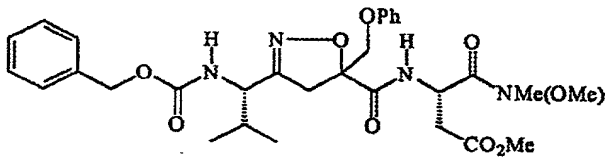
Hereinafter, the representative compounds synthesized by the process of the invention will be listed according to their structural formulae. The representative compounds according to the invention are numbered by the inventors for convenience' sake in which MP represents more polar fractions from HPLC at the previous step of deprotection while LP represents less polar fractions from HPLC. However, they are presented for the purpose of illustration of the synthesis of the compounds of the invention and for substantiating the fact that the compounds of the invention can be synthesized by the above mentioned process, but the present invention should not be limited to the listed compounds in any manner.

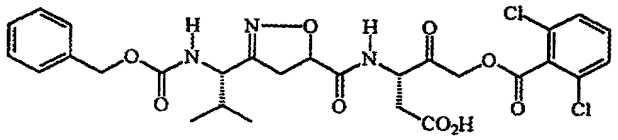
(3)  Diastereomer

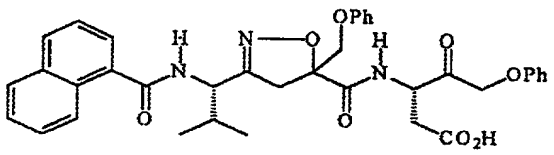
(10)  Diastereomer (less polar)

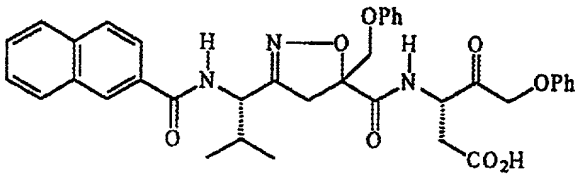
(11)  Diastereomer (more polar)

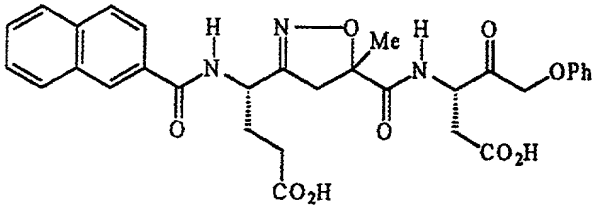
(12)  Diastereomer (less polar)

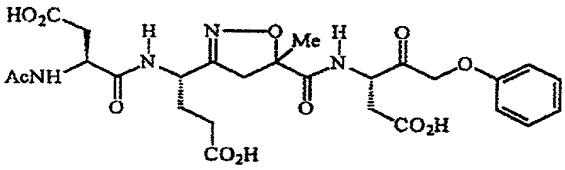
(13)  Diastereomer (more polar)

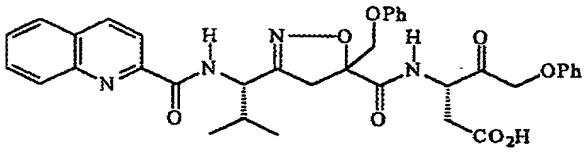
(14)  Diastereome

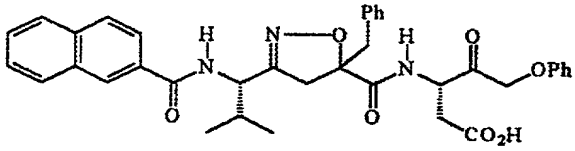
(17)  Diastereomer

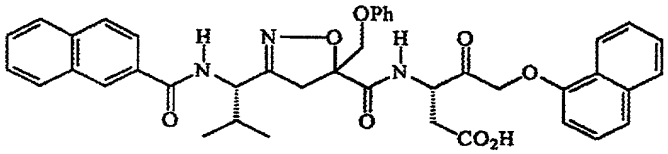
(18)  Stereoisomer

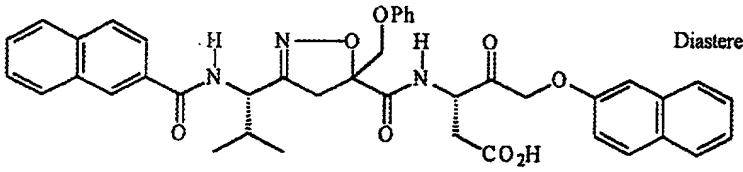
(19)  Diastereomer

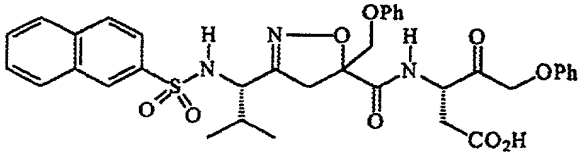
(20)  Diastereomer

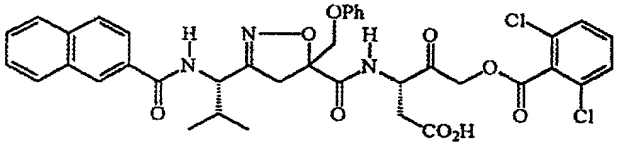
(22)  Diastereomer

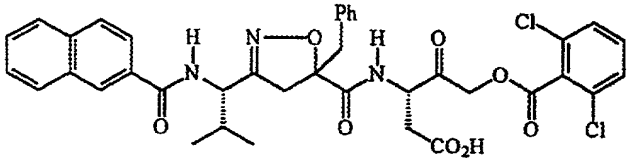
(23)  Stereoisomer

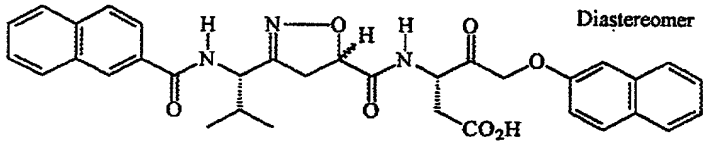
(24)  Diastereomer

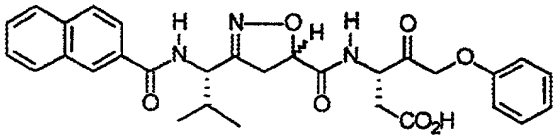
(25)  Diastereomer

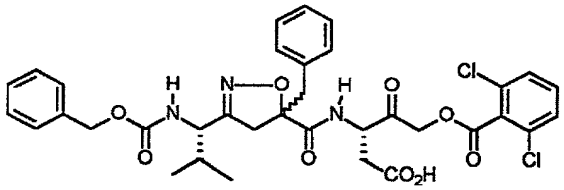
(26)  Diastereomer

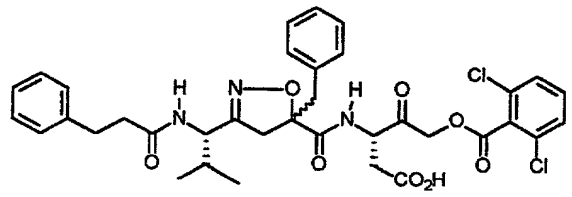
(27)  Stereoisomer

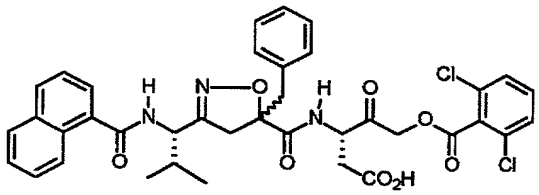
(28)  Stereoisomer

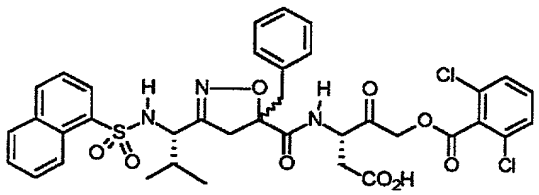
(29)  Diastereomer

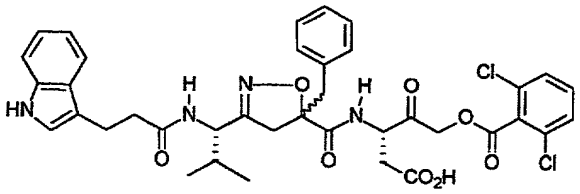
(30) 

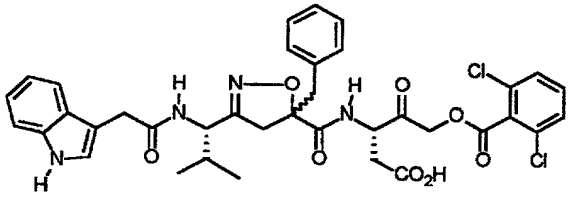
(31) 

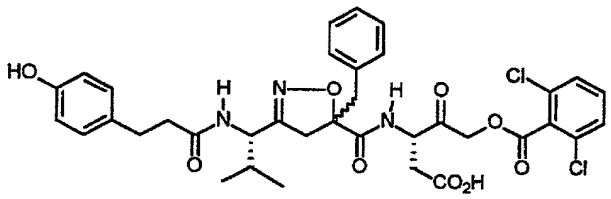
(32) 

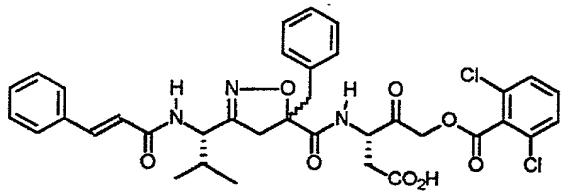
(33) 

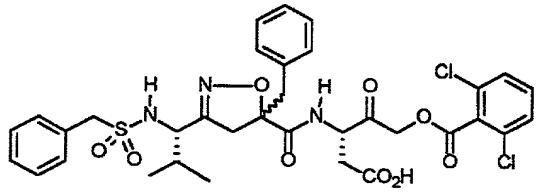
(34) 

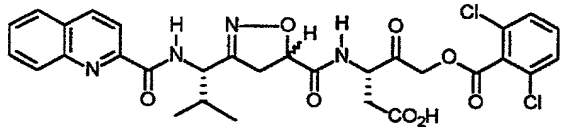
(35) 

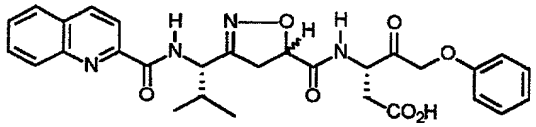
(36) 

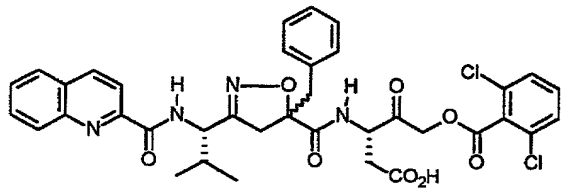
(37) 

(38) 

(39) 

(40) 

(41) 

(42) 

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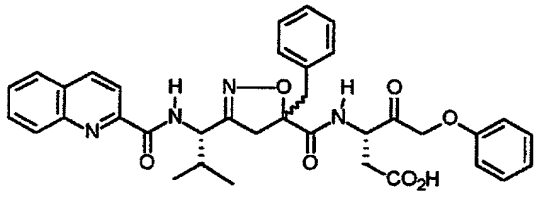

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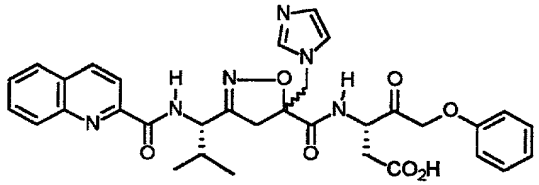

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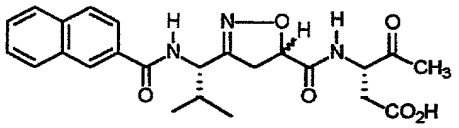

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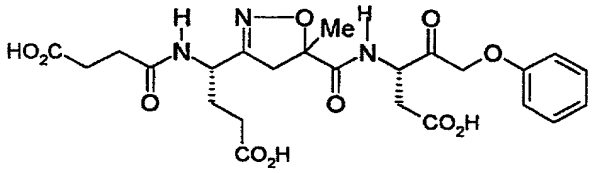

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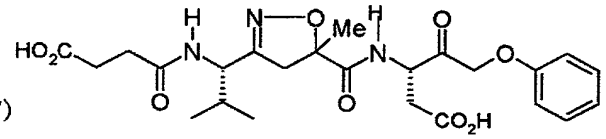

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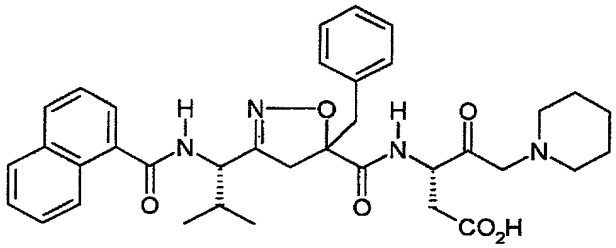
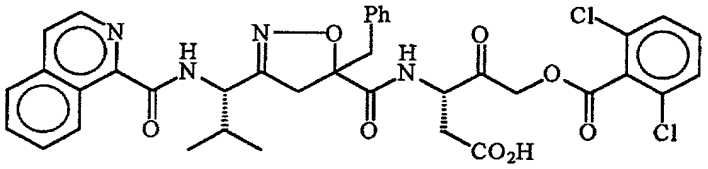
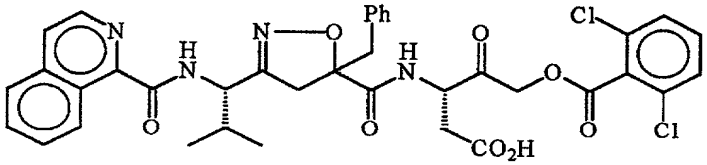
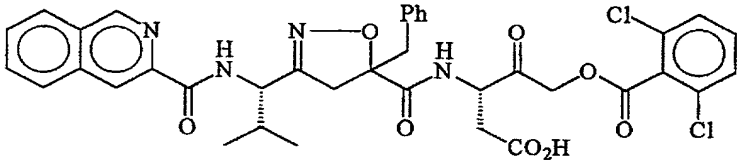
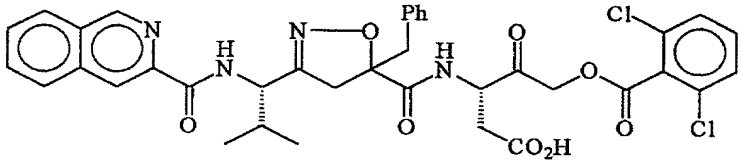
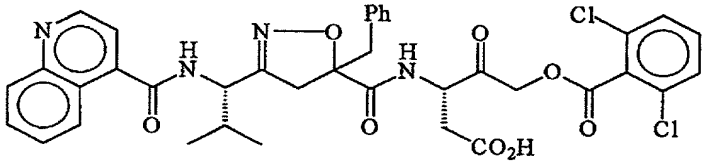


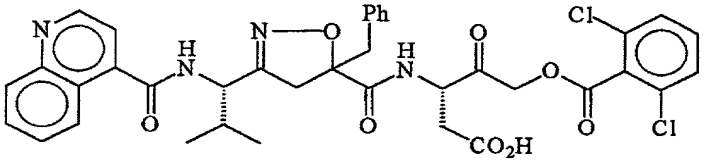
(49)  LP

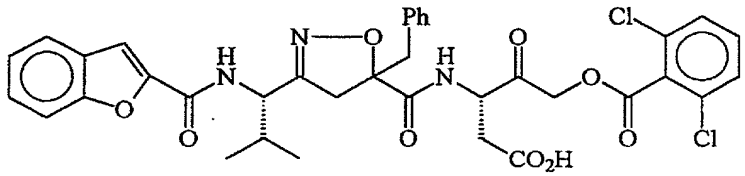
(50)  MP

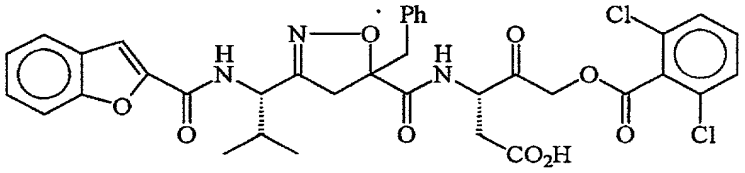
(51)  LP

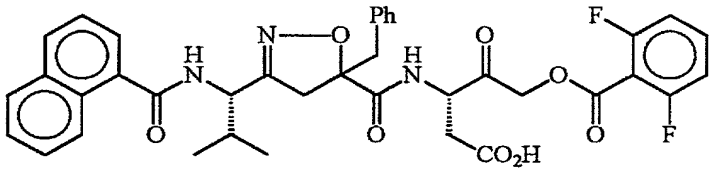
(52)  MP

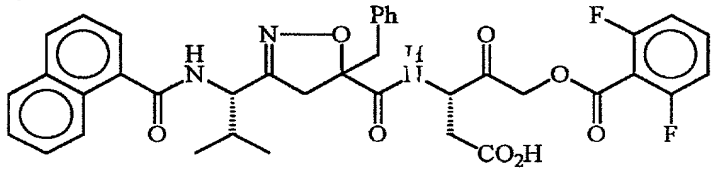
(53)  LP

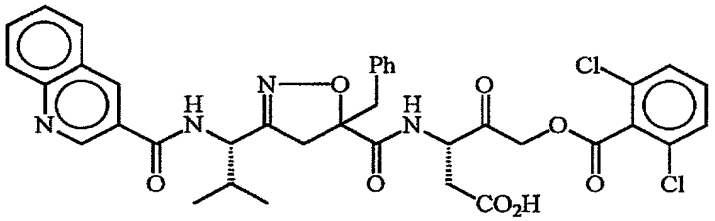
(54)  MP

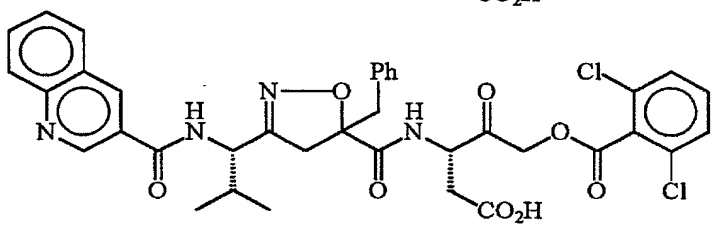
(55)  LP

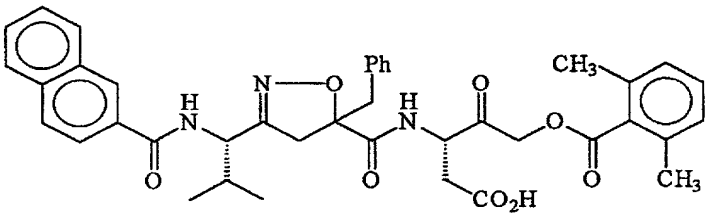
(56)  MP

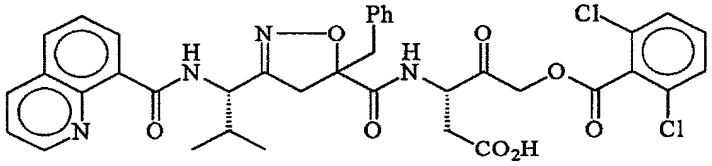
(57)  LP

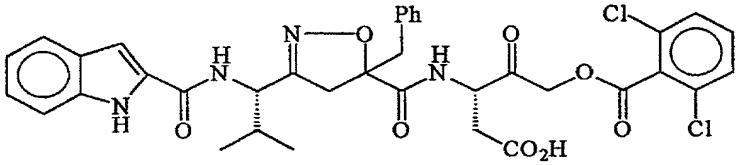
(58)  M

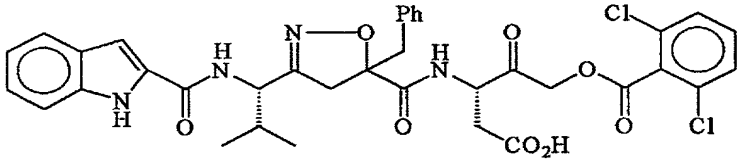
(59)  LP

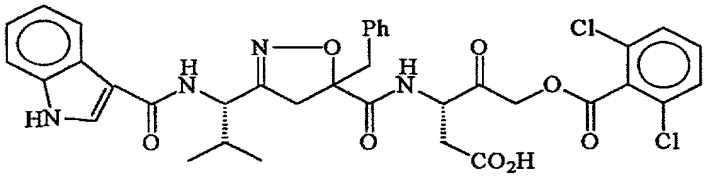
(60)  M

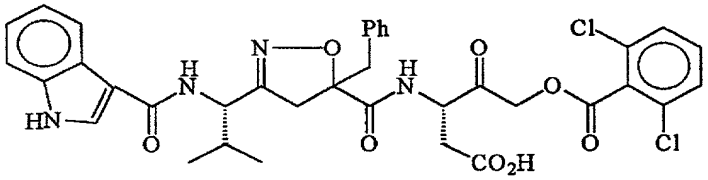
(61)  Mi

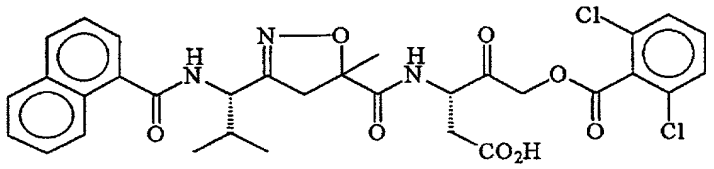
(62)  Mi

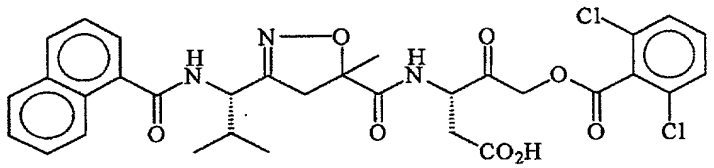
(63)  LP

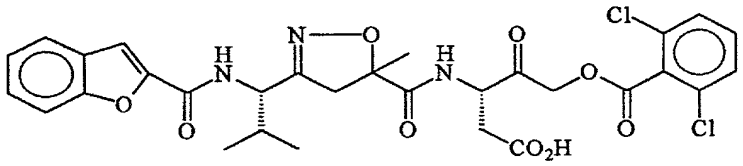
(64)  MP

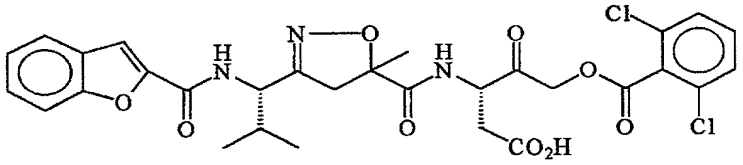
(65)  LP

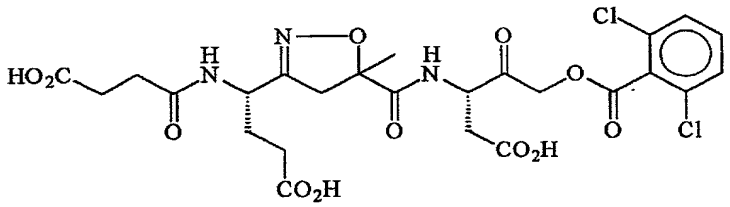
(66)  MP

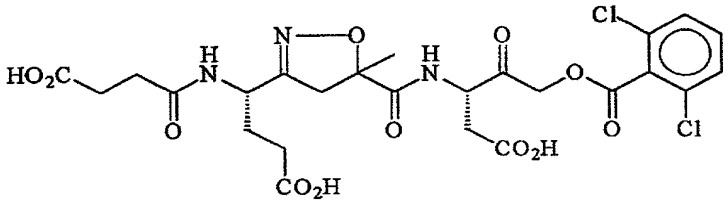
(67)  LP

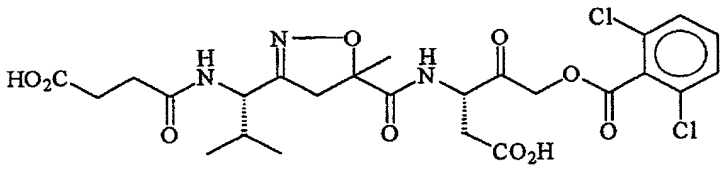
(68)  MP

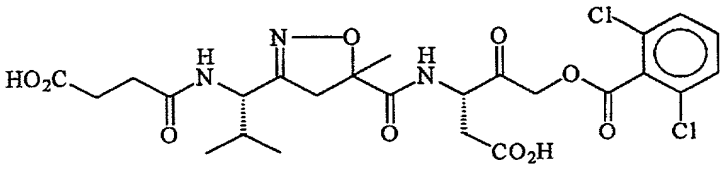
(69)  LP

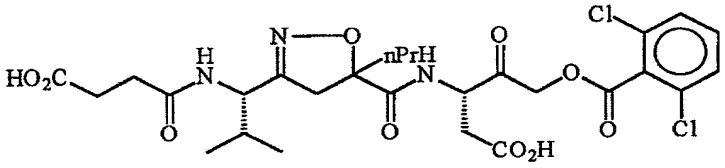
(70)  MP

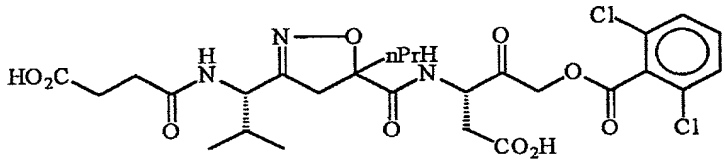
(71)  LP

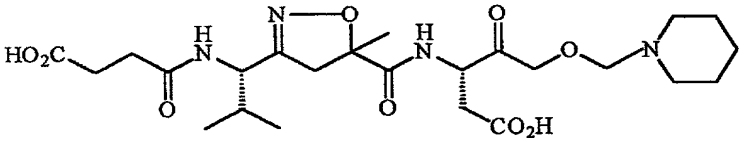
(72)  MP

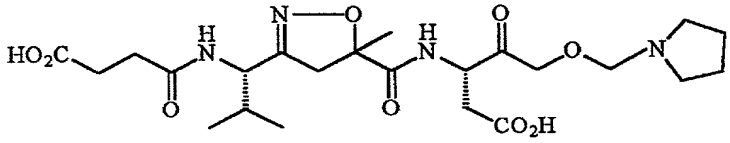
(73)  LP

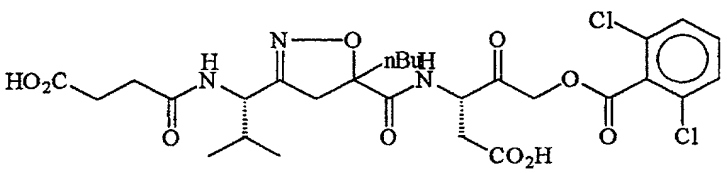
(74)  MP

(75)  LP

(76)  MP

(77)  Mi

(78)  Mi

(79) 

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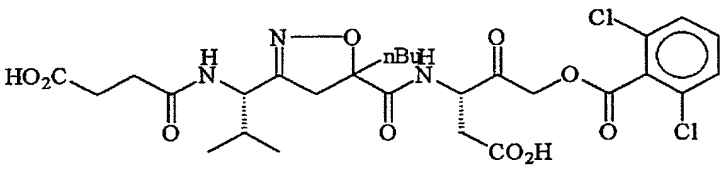
(80) 

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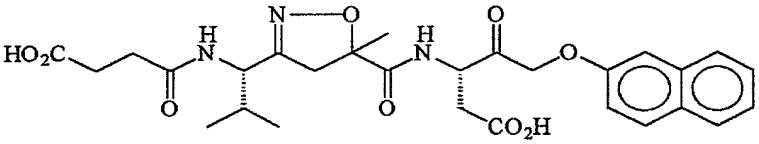
(81) 

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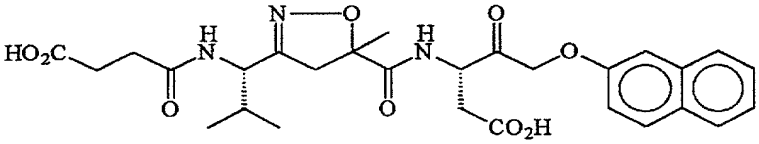
(82) 

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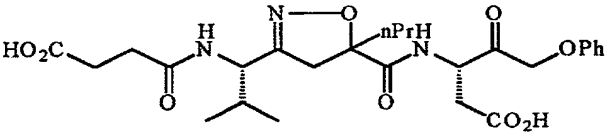
(83) 

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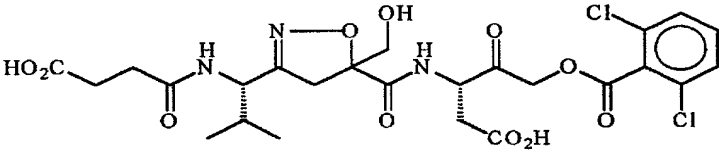
(84) 

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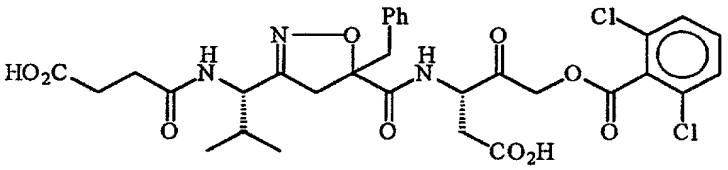
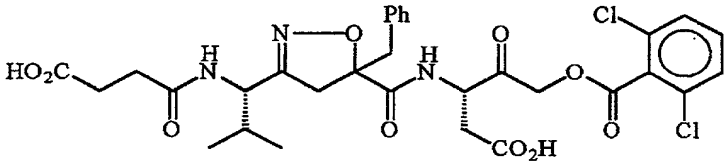
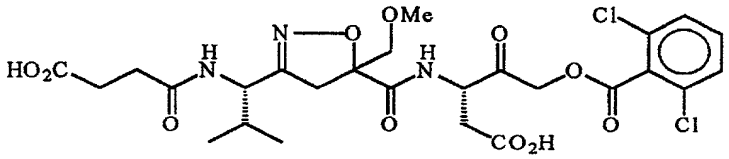
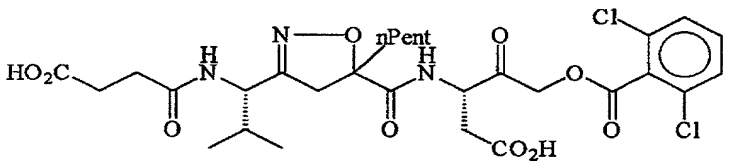
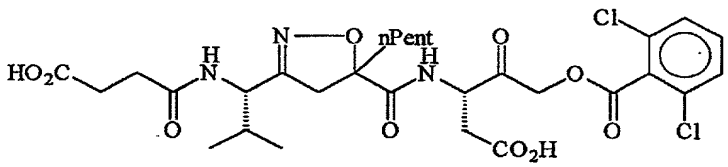
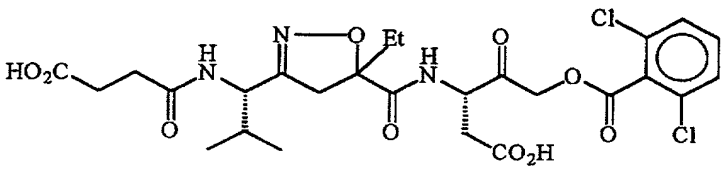
(85)  LP

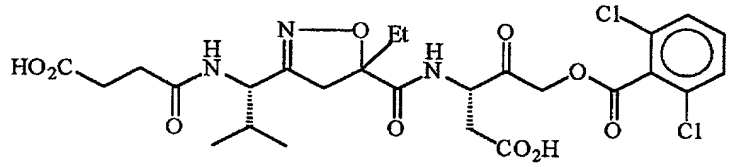
(86)  MP

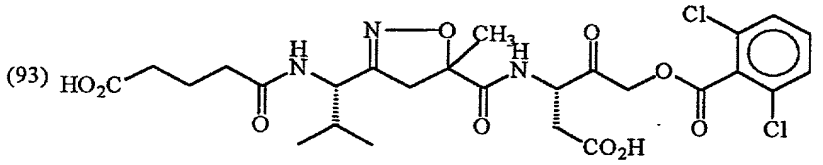
(87)  Mix

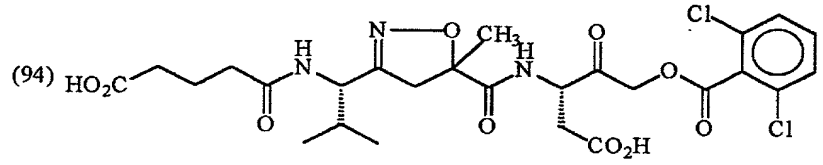
(89)  LP

(90)  MP

(91)  LP

(92)  MP

(93)  LP

(94)  MP

The isoxazoline derivative of formula (I) and the pharmaceutically acceptable salts, esters, and isomers thereof have useful pharmacological properties. For example, they have an inhibitory activity for caspases. Due to their pharmacological activity such as effects on anti-inflammation or inhibition of apoptosis, they can effectively be used as the therapeutics for a number of diseases, for example, the disease in which cells are abnormally died, dementia, cerebral stroke, brain impairment due to AIDS, diabetes, gastric ulcer, cerebral injure by hepatitis, fulminant hepatic failure (FHF), sepsis, organ transplantation rejection reaction, rheumatic arthritis, cardiac cell apoptosis due to ischaemic cardiac diseases and anti-inflammation.

In particular, the composition according to the invention can preferably be used as the therapeutics for fulminant hepatic failure.

As described in detail hereinafter, the present inventors examined, using the compound of formula (I), *in vitro* and *in vivo* caspase inhibitory activities, the viability ratio of hepatocytes in case where hepatic diseases were induced by ConA or TNF_{α} /Actinomycin D, therapeutic effect against hepatitis, reduction of hepatocytic apoptosis, and inhibition of PARP cleavage.

The present inventors have also conducted experiments on the effect of the compound of formula (I) according to the invention on cellular viability in case where apoptosis was induced by IFN_{γ} and anti-Fas antibody, and compared the results thereof with the existing caspase inhibitors, Ac-DEVD-CHO and/or z-DEVD-cmk. Briefly, we examined the efficacy of the new caspase inhibitor of formula (I) to inhibit Con A-induced acute hepatic failure in mice. As a result, this small-molecule, non-peptide-based inhibitor showed inhibition of not only caspase activities but also apoptotic death of hepatocytes *in vitro* and *in vivo*. These results suggest that the compound of formula (I) according to the present invention could be a candidate of therapeutic agent for human FHF caused by massive apoptotic death of hepatocytes.

The compound of the invention is a small-molecule, non-peptide-based caspase inhibitor which has a broad-spectrum activity (see Figures 1 & 2). The compound of formula (I) is different from BCNU or COX-2 inhibitor in the fact that it was originally designed as a specific inhibitor of caspase family enzymes. It is noteworthy that apoptotic process is very

complicated and caspases are critically involved in several steps of this process. Moreover, relatively little is known about caspase regulation largely because many of the known substrates have been found serendipitously. Thus, to block short-term, massive apoptosis of hepatocytes during acute phase of FHF, a broad-spectrum caspase inhibitor might exert more potent effect than a specific-spectrum caspase inhibitor. In this regard, the compound of formula (I) could be an ideal candidate.

The present inventors used ConA-induced hepatitis model to test the apoptosis-blocking effect of caspase inhibitor, the compound of formula (I).

Several cytokines are involved in Con A-induced hepatitis: IL-2, IFN_{γ}, TNF_{α}, IL-6, IL-4, and IL-10. The present inventors assessed the effect of the compound of formula (I) to serum IL-1β, IL-2 IL-4, and IFN_{γ} concentrations elevated by Con A. As a result, the compound of formula (I) according to the present invention significantly suppressed IL-1β level in a dose-dependent manner (see Figure 5A) due to its caspase-1-inhibiting activity shown in Figures 1 and 2. However, the compound of formula (I) did not significantly affect IL-2, IL-4, and IFN_{γ} levels (Figure 5B, C, D). These results could be attributed to the fact that the major cell population to which the compound of formula (I) exerted its activity as a caspase inhibitor is Fas-expressing hepatocytes. The compound of formula (I) rescued hepatocytes from caspase-involved apoptosis, but did not directly suppress activated T cells. One of the biosubstrates for caspase-3-like protease in cells is PARP (116 kDa) which is cleaved into 85- and 31-kDa fragments in cells undergoing apoptosis. Therefore, the appearance of an 85 kDa-cleavage product of PARP has been proposed as an early marker of apoptosis (See, Lazebnik, Y. A. et al., 1994, *Nature* 371: 346-347; Kaufmann, S. H. et al., 1993, *Cancer Res.* 53: 3976-3985).

The compound of formula (I) inhibited PARP cleavage caused by Con A-induced apoptotic death of hepatic cells in a dose-dependent manner (see Figure 7). On Western blot analysis, the amount of 85 kDa-cleavage product gradually reduced as dose of compound 33 is increased, but intact 116 kDa PARP appeared relatively constant. It is considered the hepatocytes which virtually underwent apoptosis comprise only a small portion compared with the whole liver mass. This result is consistent with histological examination. As shown in Figure 6, Con A induced severe morphological and histological changes to hepatocytes and the apoptotic lesions were clearly detectable. However, a large proportion of hepatocytes still remained alive and apoptotic cells comprise a part. This phenomenon explains the appearance of intact 116 kDa PARP even in the liver of ConA/vehicle mice.

Meantime, the present inventors induced an artificial apoptosis by treating Fas responsive cell with IFN_{γ} and anti-Fas antibody, and conducted experiments in order to evaluate the inhibitory activity of the compound of formula (I) on the cells against apoptosis. As a result, the inventors discovered that the compound of formula (I) revealed 2-fold or more superior inhibitory effect over the known Ac-DEVD-CHO or z-DEVD-cmk (At the same concentration, the cell viability was 35.1%(Ac-DEVD-CHO) , 47.3%z-DEVD-cmk, and 100%(Compound 33), see Table 1 and Fig. 8).

From the above experiment results, it is noted that the non-peptidic compound of formula (I) has a wide variety of caspase inhibitory activities and thus, anti-inflammation and apoptosis prevention effects, especially can effectively be used as therapeutics for preventing massive apoptosis of hepatocytes in human FHF.

The compound of formula (I) is a new, non-peptide based caspase inhibitor. Its broad-spectrum activity could be a beneficial property as a therapeutic agent blocking the massive apoptosis of hepatocytes in human FHF.

The compounds of the present invention, therefore, may be used as medicines against above-mentioned diseases. Said use as a medicine or method of treatment comprises local or systemic administration to patients of an effective amount of the compounds according to the invention for treating the diseases.

The subject compounds may be formulated into various pharmaceutical forms for administration purposes. Said pharmaceutical forms or compositions are deemed to novel and consequently constitute a further aspect of the present invention. Also the preparation of said composition constitutes a further aspect of the present invention. To prepare the pharmaceutical composition of this invention, an effective amount of the compound, in base or salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier which may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, percutaneously, or by parenteral injection. It is especially advantageous to formulate the above pharmaceutical composition in unit dosage form for ease of administration and uniformity of dosage. For example, in preparing the composition in oral dosage form, any of the usual pharmaceutical media may be employed for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as

suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agent and the like in the case of powders, pills, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. It is preferable that tablets and fills are enteric-coated.

For parenteral compositions, the carrier will usually include sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example sterilized aqueous injection suspension or oil suspension, may be prepared with suitable dispersing agents, wetting agents or suspending agents. Solvents which can be used for this purpose include water, Linger's solution, isotonic NaCl solution, etc. Sterilized fixed oils can also be used as a solvent or a suspending medium. Any non-excitatory fixed oils including mono-, diglycerides can be used for this purpose and fatty acids such as oleic acid can be used in the injectable preparation.

In the preparation suitable for percutaneous administration, the carrier optionally includes a penetration enhancing agents and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, wherein the additives do not give a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may assist preparation of the desired compositions. These compositions may be administered in various routes, e.g., as a transdermal patch, as a spot-on or as an ointment.

Dosage unit as used in the specification and claims herein refers to physically discrete units suitable as unitary dosage, each unit containing a

predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets, capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In view of the usefulness of the subject compounds in the treatment of the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation, it is evident that the present invention provides a method of treating patients suffering from the diseases, which comprises the local or systemic administration of a pharmaceutically effective amount of the compound of formula (I) or the pharmaceutically acceptable salt, ester or stereochemically isomeric form thereof in admixture with a pharmaceutical carrier.

Those skilled in the treatment of the diseases associated could easily determine the effective amount of the caspase inhibitor, especially the compound of formula (I) to be administered into a subject. In general, it is contemplated that an effective amount would range from 0.01 mg/kg to 100 mg/kg body weight a day in a unit dosage or divided dosage. However, it is evident to those skilled in the art that such amount ranges are guidelines only and are not intended to limit the scope or use of the invention in any manner. The specific dosage level for a specific subject would depend upon the particular compound to be employed, weight of a subject, health conditions, regimen, administration period of the drug, administration route, excretion rate, combination of drug, the severity of diseases, etc.

The present invention will be described in greater detail through the following examples. The examples are presented for illustrating purposes only and should not be construed as limiting the invention which is properly delineated in the claims.

EXAMPLES

(A) Hydroxamoyl chloride synthesis (Examples 1 to 4)

Example 1: Synthesis of N-t-butoxycarbonyl-(S)-valinal and N-t-butoxy-carbonyl-(S)-valinal oxime

To a solution of dimethyl sulfoxide (11.7 mL, 3.0 eq) in dry CH_2Cl_2 (~200 mL) under N_2 at -60 °C was added slowly oxalyl chloride (5.78 mL, 1.2 eq). After 10 min., a solution of N-t-butoxycarbonyl-(S)-valinol (11.23g, 55.2 mmol) in CH_2Cl_2 (30 mL) was added slowly, and the flask was rinsed with 20 mL of CH_2Cl_2. The resulting white suspension was stirred for 1h at ~ -50 °C. The reaction solution was treated with diisopropylethylamine (28.8 mL, 3.0 eq) and stirred for about 20 min. at -23 °C then diluted with hexanes (400 mL). The mixture was washed with water(150 mL), 1N-$KHSO_4$ solution (x 3, total 1 L), dried with anhydrous Na_2SO_4, filtered and concentrated. The yellowish liquid obtained was used directly in next step without further purification.

The crude valinal in ethanol (60 mL)-water (30 mL) at water bath temperature was treated with hydroxylamine hydrochloride (5.76g, 1.5 eq) and Na_2CO_3 (4.39g, 0.75 eq.). The reaction generated a lot of solid in 1 min., thus diluted with ethanol-water (1:1, 60 mL) and stirred for 1h. The reaction solution was poured into saturated NaCl (100 mL), and then

extracted with ethyl acetate twice (300 mL). Organic extracts were washed with sat'd $NaHCO_3$ (100mL x 2), dried (anh. Na_2SO_4), filtered and concentrated to yield white powder (11.34g, syn, anti mixture of oximes).

Example 2: Synthesis of (2S)-2-(t-butoxycarbonyl)amino-1-chloro-3-methyl-butane-1-one oxime

N-t-butoxy-carbonyl-(S)-valinal oxime (11.34g) in DMF (100 mL) was treated with NCS (7.75g) and stirred in warm water bath (~40 °C) for 1h. After removal of DMF, the residue was extracted with ethyl acetate-hexanes (1:1, 150 mL), washed with water (100 mL x 3), dried (anh. Na_2SO_4), filtered and concentrated to give 13.69g of the title compound.

Example 3: Synthesis of 4-(9-fluorenylmethoxycarbonyl)amino-(4S)-5-hydroxy-pentanoic acid t-butyl ester

To a solution of N-(9-fluorenylmethoxycarbonyl)-$_\gamma$ -t-butyl glutamic acid (8.51g, 20.0 mmol) and NMM (2.42mL, 1.1 eq) in dry THF (110 mL) under N_2 at 0 °C was added isobutyl chloroformate (2.72mL, 1.05eq). After 20 min., the reaction mixture was filter-added to a solution of $NaBH_4$ (1.5g) in THF (120mL)-MeOH (30 mL) at -78 °C under N_2 and rinsed with dry THF (20mL). After stirring for 2.5h at -78 °C, the reaction was quenched with acetic acid (13mL). After concentrating to ~ 50mL, the residue was dissolved in ethyl acetate-hexanes (200 mL,1:1), washed with water (150 mL x 2). Aqueous layer was re-extracted with ethyl acetate-hexanes (150 mL,1:1). Combined extract was washed with sat'd $NaHCO_3$ (150 mL x 2), dried (anhydrous Na_2SO_4), filtered and concentrated to give 8.30g of the title compound as glasslike solid. The

crude alcohol was used directly.
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.77 (2H, d, J=7.3Hz), 7.66 (2H, d, J = 7.8 Hz), 7.41 (2H, t, J = 7.3 Hz), 7.31 (2H, pseudo t, J = 7.8, 7.3 Hz), 5.18 (NH, d), 4.41 (2H, m), 4.22 (1H, m), 3.72-3.57 (3H, m), 2.33 (2H, m), 1.93-1.77 (2H, m), 1.45(9H, s).

Example 4: Synthesis of 4-(9-fluorenylmethyloxycarbonyl)amino-(4S)-5-chloro-5- hydroxyimino-pentanoic acid t-butyl ester

To a solution of DMSO (3.0 mL) in dry CH_2Cl_2 (100 mL) at -65°C under N_2 was added oxalyl chloride (2.10 mL, 1.2eq) slowly. After 15 min., a solution of 4-(9-fluorenylmethyloxycarbonyl)amino-(4S)-5-hydroxypentanoic acid t-butyl ester (8.30 g, 20 mmol) in CH_2Cl_2 (50 mL) was added and rinsed with dry CH_2Cl_2 (20 mL). The resulting solution was stirred for 2h at -40 ~ -50 °C. EtN(i-Pr)$_2$ (10.45 mL, 3.0eq) was added thereto and the reaction solution was slowly warmed up to -10 °C with TLC checking (conversion to aldehyde is relatively slow, ~1h). The reaction mixture was diluted with hexanes (300 mL), washed with water(150 mL), with 1N-$KHSO_4$ (x 3, total 500 mL), dried with anh. Na_2SO_4, filtered and concentrated to give the corresponding aldehyde.

The crude aldehyde in ethanol(60 mL)-CH_2Cl_2 (30 mL)-water(10 mL) at 0°C was treated with $H_2NOH \cdot HCl$ (2.08 g, 1.5eq) and Na_2CO_3 (1.60g, 0.75 eq). The reaction was stirred at room temperature for 30 min., then water (10 mL) was added and stirred for additional 1h. The reaction was stirred further(1h) with additional $H_2NOH \cdot HCl$ (400 mg) and Na_2CO_3 (320 mg). Most of the volatiles were removed in vacuo, and the residue was taken up with ethyl acetate (200 mL), washed with water(100 mL), sat'd $NaHCO_3$ (100 mL), dried (anh. Na_2SO_4), filtered and concentrated to

give the desired oxime (8.30g, syn + anti) as white powder.

The crude oxime in DMF (35 mL) was treated with NCS (2.67g, 20.0 mmol). The reaction was stirred in warm (40°C) bath for 1h. After removal of the DMF in high vacuum rotary evaporator, the residue was taken up with hexane-ethyl acetate (1:1, 150 mL), washed with water (100 mL x 3), dried (anh. Na_2SO_4), filtered and concentrated to give the title compound (9.25g, syn + anti).

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.88(1H, s), 7.75(2H, d, J = 7.3Hz), 7.57(2H, m), 7.39(2H, t, J = 7.32Hz), 7.30 (2h, pseudo t, J = 7.8,7.3Hz), 5.46(1H, d), J = 9.3 Hz), 4.63(1H, m), 4.43-4.38(2H, m), 4.19(1H, m), 2.3(2H, m), 2.03(2H, m), 1.43(9H, s). (NMR data reported for major isomer.)

The Following compounds were prepared in the same manner as the above examples.

· 1-chloro-3-methyl-(2S)-2-phenylmethyloxycarbonylamino-butane-1-one oxime,

· 3-(t-butoxycarbonylamino)-(3S)-4- chloro-4-hydroxyimino-butanoic acid methyl ester,

· 3-(phenylmethyloxycarbonylamino)-(3S)-4-chloro-4-hydroxyimino-butanoic acid t-butyl ester, and

· 3-(9-fluorenylmethyloxycarbonylamino)-(3S)-4-chloro-4-hydroxyimino-butanoic acid t-butyl ester.

(B) Synthesis of acrylate derivatives (Examples 5 to 8)

Example 5: Synthesis of ethyl 2-acetoxymethylacrylate

A solution of ethyl 2-hydroxymethyl acrylate (17.3g, 133 mmol, purity ~ 70%, ref: Villieras, J. and Rambaud, M. Synthesis, 1982, *914*) in dry CH_2Cl_2 (200 mL) under N_2 at 0 °C was treated with acetic anhydride (18.8 mL, 1.5 eq) and triethyl amine (37 mL, 2.0 eq). After overnight stirring at room temperature, the reaction was diluted with hexanes (400 mL), washed with sat'd $NaHCO_3$ (300 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. Simple distillation gave 4.6g of the title compound as clear liquid. NMR analysis showed ~ 70 % purity.
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.36 (1H, s), 5.84 (1H, s), 4.81(2H, s), 4.25 (2H, q, J = 7.3 Hz), 2.11 (3H, s), 1.31 (3H, t, J = 7.3 Hz)

Example 6: Synthesis of ethyl 2-phenoxymethylacrylate

A solution of ethyl 2-bromomethylacrylate (2.00g, 10.4 mmol, ref: Villieras, J. and Rambaud, M. Synthesis, 1982, *914*) and phenol(975 mg, 1.0eq) in dry THF (20 mL) under N_2 at 0 °C was treated with anhydrous K_2CO_3 (1.43g, 1.0 mol eq). No reaction was observed for 1h. Anhydrous DMF (20 mL) was added and stirred for 2h at 0 °C and for 1h at room temperature. After evaporation of DMF, water(100 mL) was added, and the reaction was extracted with ethyl acetate (100 mL x 2). The organic extract was washed with brine (100 mL), dried (anh. Na_2SO_4), filtered and concentrated. Flash chromatography (40% CH_2Cl_2/hexanes) gave 1.712g (80%) of the title compound.
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.30 (2H, yt, J = 7.3 Hz), 6.99-6.96 (3H, m), 6.41 (1H, s), 6.01 (1H, s), 4.78 (2H, s), 4.27 (2H, q, J = 7.33 Hz)

Example 7: Synthesis of ethyl 2-benzylacrylate
To a solution of bromobenzene (7.15g, 45.5 mmol) in THF (30mL) was added n-BuLi (16.6mL, 2.5M in Hexane, 41.4mmol) under N_2 at -78 °C.

It was stirred for 10min. To a suspension of CuCN (3.71g, 41.4mmol) in THF (30mL) was added lithiated benzene solution via cannula under N_2 at -78 °C. The reaction mixture was stirred for another 10 min. at -78 °C and ethyl 2-bromomethyl acrylate (4.00g, 20.7 mmol) in THF was added. The reaction mixture was warmed up to room temperature slowly and quenched with 2N HCl. All precipitates were filtered off and the filtrate was diluted with hexanes (400 mL), washed with sat'd $NaHCO_3$ (300 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. Flash chromatography (2% ethyl acetate-hexanes) gave 3.04g(77%) of the title compounds .
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (5H, m), 6.26 (1H, s), 5.48(1H, s), 4.22(2H, q, J = 6.3Hz), 3.66 (2H, s), 1.29 (3H, q, J = 6.3 Hz).

Example 8: Synthesis of ethyl 2-(4-bromophenyl)acrylate

The title compound was prepared according to the known procedure (Helvetica Chimica Acta 1986, *69* 2048).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.46 (2H, d), 7.29 (2H, d), 6.37 (1H, s), 5.90 (1H, s), 4.29 (2H, q), 1.33 (3H, t)

The following compounds were similarly prepared.

· Ethyl 2-(1-naphthyl)acrylate
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.86 (2H, t, J = 7.3 Hz), 7.44 (1H, d, J = 8.8 Hz), 7.48-7.43 (3H, m), 7.37 (1H, d, J = 6.8 Hz), 6.70 (1H, d, J = 2.0 Hz), 5.89 (1H, d, J = 2.0 Hz), 4.22 (2H, q, J = 7.3 Hz), 1.21 (3H, t, J = 7.3 Hz),

· Ethyl 2-(2-naphthyl)acrylate
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.95 (1H, s), 7.90-7.86 (3H, m), 7.59-7.52 (3H, m), 6.47 (1H, d, J = 1.0Hz), 6.06 (1H, d, J = 1.0 Hz), 4.38 (2H, q,

J = 6.8 Hz), 1.40 (3H, t, J = 6.8Hz).

Ethyl 2-butyl acrylate

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.11 (s, 1H), 5.49 (d, J = 1.4 Hz, 1H), 4.19 (q, J = 6.9 Hz, 2H), 2.29 (m, 2H), 1.45-1.28 (m, 7H), 0.90 (t, J = 7.3 Hz, 3H).

Ethyl 2-propyl acrylate

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.12 (d, J = 0.9 Hz, 1H), 5.49 (d, J = 1.4 Hz, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.27 (m, 2H), 1.49 (m, 2H), 1.29 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).

Ethyl 2-ethyl acrylate

^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.11 (d, J = 0.9 Hz, 1H), 5.50 (s, 1H), 4.20 (q, J = 6.9 Hz, 2H), 2.32 (m, 2H), 1.29 (t, J = 6.9 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H).

Ethyl 2-pentyl acrylate

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 1H), 5.50 (s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.29 (m, 2H), 1.51-1.13 (m, 9H), 0.89 (t, J = 6.8 Hz, 3H).

(C) General procedure for isoxazoline synthesis (Examples 9 and 10)

Example 9: Synthesis of 3-((1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl)-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

A solution of (2S)-2-phenylmethyloxycarbonylamino-1-chloro-3-methyl-butane-1-one oxime (640 mg, 2.25mmol) and ethyl 2-phenoxymethylacrylate (464mg) in dry ether(10 mL) under N_2 at -78°C was treated with

triethylamine (627 uL, 2.0 eq). The reaction was stirred overnight, allowing to warm up to room temperature slowly. Water(100 mL) was added, and the reaction was extracted with ethyl acetate (100 mL x 2), washed with water(100mL), dried (anh. Na_2SO_4), filterd and concentrated. Flash chromatography (15% ethyl acetate-hexanes) gave 851mg(83%) of the title compounds as 1:1 mixture of diastereomers.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.34(7H, m), 6.98 (1H, t, J = 7.3Hz), 6.89 (2H, d, J = 7.7Hz), 5.61 (1H, d, J = 9.3 Hz), 5.15-5.08 (2H, m), 4.50 (1H, br s), 4.33-4.22 (4H, m), 3.60-3.54(1H, m), 3.32-3.27(1H, m), 2.10 (1H, m), 1.29 (3H, m), 1.02-0.94 (6H, m).

The following compounds were prepared similarly:

· Ethyl 3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.45-7.15 (m, 10H), 5.07 (m, 2.5H), 4.90 (d, 0.5H), 4.30-4.18 (m, 3H), 3.36-2.88 (m, 4H), 1.95-1.80 (m, 1H), 1.27 (m, 3H), 0.86-0.55 (m, 6H).

· 3-[(1S)-1-t-butoxycarbonylamino-2-methyl-propyl]-5-(2-naphthyl)-4,5-di-hydro-isoxazole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.97(1H, s), 7.86-7.82 (3H, m), 7.52-7.48 (3H, m), 4.93 (1H, br), 4.37 (1H, m), 4.25 -4.18 (2H, m), 4.10-4.05 (1H, two doublets, J=17.1, 17.6 Hz), 3.28-3.22 (1H, two doublets, J = 17.1, 17.1 Hz), 2.05 (1H, m), 1.43 ((H, s), 1.24-1.20 (3H, m), 0.98-0.91 (6H, m).

· 3-[(1S)-1-t-butoxycarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihyd ro-isoxazole-5-carboxylic acid ethyl ester (~1:1 diastereomers)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.25 (5H, m), 4.82 and 4.60 (1H, two m), 4.25-4.15 (3H, m), 3.38-3.29 (2H, m), 3.10 (1H, m), 2.90 (1H, m), 1.43 and 1.42 (9H, two s), 1.27 (3H, m), 0.90-0.80 (6H, m).

· 5-acetoxymethyl-3-[(1S)-1-t-butoxy-carbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, br), 4.44-4.26 (5H, m), 3.50 (1H, m), 3.10 (1H, m), 2.08 (4H, s + br 1H), 1.46 (9H, s), 1.32-1.30 (3H, m), 1.02-0.96 (6H, m).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.96 & 4.87 (two br s, 1H), 4.34-4.18 (m, 3H), 3.42-3.36 (m, 1H), 2.90-2.83 (m, 1H), 2.02 (m, 1H), 1.91 (m, 2H), 1.43 (s, 9H), 1.37-1.26 (m, 7H), 0.98-0.87 (m, 9H).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.96-4.86 (m, 1H), 4.33-4.18 (m, 3H), 3.42-3.36 (m, 1H), 2.90-2.83 (m, 1H), 2.02 (m, 1H), 1.89 (m, 2H), 1.43 (s, 9H), 1.29 (m, 5H), 0.98-0.87 (m, 9H).

· Methyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-methoxymethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.92 (m, 1H), 4.35 (m, 1H), 3.80 & 3.79 (two s, 3H), 3.40 (s, 3H), 3.88-3.13 (m, 4H), 2.04 (m, 1H), 1.44 (s, 9H), 0.99-0.91 (m, 6H).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.95& 4.88 (two br s, 1H), 4.30-4.17 (m, 3H), 3.42-3.36 (m, 1H), 2.89-2.83 (m, 1H), 2.02 (m, 1H), 1.90 (m, 2H), 1.43 (s, 9H), 1.28 (m, 9H), 0.98-0.85 (m, 9H).

· Ethyl 3-[2-methyl-(1S)-1-(tert-butyloxycarbonylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
1H-NMR (500 MHz, $CDCl_3$) δ 4.96& 4.88 (two br s, 1H), 4.31-4.18 (m, 3H), 3.42-3.36 (m, 1H), 2.89-2.80 (m, 1H), 2.03 (m, 1H), 1.94 (m, 2H), 1.43 (s, 9H), 1.29 (m, 3H), 0.97-0.86 (m, 9H).

Example 10: Synthesis of 3-[(1S)-1-(9-fluorenylmethyloxycarbonylamino)-3-t-butoxycarbonyl-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester

A solution of 4-(9-fluorenylmethoxycarbonyl)amino-(4S)-5-chloro-5-hydroxy-imino-pentanoic acid t-butyl ester (3.44g, 7.50 mmol) and methyl methacrylate (2.40mL, 3.0 eq) in dry ether under N_2 at -78 °C was treated with $EtN(i\text{-}Pr)_2$ (1.96mL, 1.5eq). Similar treatment as described previously followed by flash chromatography with 25-30% ethyl acetate/hexanes gave 3.46g (89% overall) of the title compound as diastereomeric mixture.
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.77 (2H, d, J=7.3Hz), 7.59 (2H, d, J =7.3Hz), 7.40 (2H, t, J = 7.3Hz), 7.31 (2H, t, J =7.3 Hz), 5.34 (1H, m), 4.58-4.38 (3H, m), 4.21 (1H, m), 3.78 (3H, s), 3.48 (1H, m), 2.90-2.81 (1H, m), 2.42-2.27 (2H, m), 2.18 (1H, m), 1.93 (1H, m), 1.63 (3H, s),

1.45 (9H, s)

(D) Transformations of isoxazolines (Deprotection, Introduction of P_4 group, Hydrolysis of ester group) (Examples 11 and 12)

Example 11: Synthesis of 3-{2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl}-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

A solution of 3-{(1S)-1-(t-butoxycarbonylamino)-2-methyl-propyl}-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (2.00g, 4.76 mmol) in dry CH_2Cl_2 (10 mL) at 0°C under N_2 was treated with TFA (6 mL) and stirred for 1.5h. After removal of volatiles, the residue was taken up with ethyl acetate (200 mL), washed with sat'd $NaHCO_3$ (100 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. To a solution of the crude product, EDC (1.09g, 1.2 eq), 2-naphthoic acid (983 mg, 1.2 eq) and HOBt (771 mg, 1.2 eq) in DMF (20 mL) at 0°C was added triethylamine (663 uL, 1.0 eq). The reaction was stirred overnight at room temperature. After removal of volatiles in vacuo, the residue was taken up with ethyl acetate (250 mL), washed with water(100 mL), sat'd $NaHCO_3$ (100 mL x 2), dried (anh Na_2SO_4), filtered and concentrated. Flash chromatography with 25-33% ethyl acetate/hexanes gave 2.04g (90%) of the title compound.
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H,s), 7.93-7.84 (4H, m), 7.58-7.52 (2H, m), 7.29-7.22 (2H, m), 7.00-6.81 (4H, m), 5.06-5.01 (1H, m), 4.36-4.24 (4H, m), 3.68-3.61 (1H, m), 3.43-3.39 (1H, m), 2.28 (1H, m), 1.31-1.26 (3H, m), 1.12-1.05 (6H, m).

Hydrolysis of isoxazoline 5-carboxylic acid ester: The above compound

(2.04g) in distilled THF (40 mL) (not completely soluble) was treated with 1N-NaOH(5.2 mL, 1.2 eq). After 4h (~50% completion), additional 1N-NaOH (1.0 mL) was added. After stirring overnight, the reaction was neutralized with concentrated 1N-HCl. The residue was taken up with CH_2Cl_2 (>700 mL), washed with water, dried (anh Na_2SO_4), filtered and concentrated to give 1.948g (103%) of the free carboxylic acid, which was used directly in next step.

The following compounds were prepared similarly:

· 3-{2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl}-5-phenoxymethyl -4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.23 (1H, d, J = 8.3 Hz), 7.93-7.86 (2H, m), 7.66 (1H, m), 7.54-7.42 (3H, m), 7.29-7.25 (2H, m), 7.00-6.90 (3H, m), 6.49 (1H, m), 5.13-5.09 (1H, m), 4.40-4.26 (4H, m), 3.69-3.64 (1H, m), 3.44-3.41 (1H, m), 2.28 (1H, m), 1.32-1.01 (9H, m).

· 3-{2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl}-4,5-dihydro-isoxa zole-5-carboxylic acid ethyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H, s), 7.94-7.83 (4H, m), 7.59-7.53 (2H, m), 6.80-6.70 (NH, two d), 5.07-5.03 (2H, m), 4.28-4.21 (2H, m), 3.37-3.33 (2H, m), 2.28 (1H, m), 1.34-1.25 (3H, m), 1.12-1.02 (6H, m).

· 3-[(1S)-1-(1-naphthalenecarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4, 5- dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.28 (d, J = 7.8 Hz, 1H), 7.94-7.86 (m, 2H), 7.61-7.11 (m, 9H), 6.36 (d, J = 9.3 Hz, 0.5H), 6.09 9d, J = 9.3 Hz, 0.5H), 4.94-4.85 (m, 1H), 4.27-4.21 (m, 2H), 3.49-2.98 (m, 4H), 2.15 &

1.97 (two m, 1H), 1.30-1.26 (m, 3H), 1.03-0.59 (m, 6H).

· Ethyl 3-[(1S)-1-phenethylcarbonylamino-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.28-7.17 (m, 10H), 5.74 & 5.50 (two d, J = 9.3 Hz, NH), 4.58-4.52 (m, 1H), 4.24-4.20 (m, 2H), 3.34-3.25 (m, 2H), 3.11-2.82 (m, 4H), 2.52-2.45 (m, 2H), 1.93 &1.75 (two m, 1H), 1.29-1.25 (m, 3H), 0.79-0.41 (m, 6H).

· 3-[(1S)-1-(1-naphthalenesulfonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68-8.64 (m, 1H), 8.29-8.25 (m, 1H), 8.07 (m, 1H), 7.93 (m, 1H), 7.71-7.52 (m, 3H), 7.23-6.98 (m, 5H), 5.27 & 5.19 (two m, 1H), 4.12-4.07 (m, 2H), 3.75 & 3.66 (two m, 1H), 3.16-2.43 (m, 4H), 1.77-1.62 (m, 1H), 1.25-1.16 (m, 3H), 0.86-0.57 (m, 6H).

· 3-[(1S)-1-(indole-3-yl-ethylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5 -dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.16-8.12 (m, 1H), 7.62-7.56 (m, 1H), 7.36-6.94 (m, 9H), 5.71 (d, J = 9.3 Hz, 0.5H), 5.42 (d, J = 8.8 Hz, 0.5H), 4.56-4.50 (m, 1H), 4.25-4.17 (m, 2H), 3.30-2.51 (m, 8H), 1.89-1.70 (m, 1H), 1.28-1.24 (m, 3H), 0.73-0.41 (m, 6H).

· 3-[(1S)-1-(indole-3-yl-methylcarbonylamino)-2-methyl-propyl]-5-phenylmeth yl-4,5 -dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.56 & 8.52 (two br s, 1H), 7.55-7.05 (m, 10H), 5.98-5.91 (m, 1H), 4.57 (m, 1H), 4.22-4.15 (m, 2H), 3.73 (m, 2H), 3.28-2.79 (m, 4H), 1.87-1.68 (m, 1H), 1.27-1.20 (m, 3H), 0.75-0.34

(m, 6H).

· 3-[(1S)-1-(cinnamoylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61-7.23 (m, 11H), 6.40-6.34 (m, 1H), 6.06 (d, J = 8.8 Hz, 0.5H), 5.81 (d, J = 9.3 Hz, 0.5H), 4.76-4.69 (m, 1H), 4.26-4.19 (m, 2H), 3.42-2.94 (m, 4H), 2.06 & 1.88 (two m, 1H), 1.28-1.24 (m, 3H), 0.93-0.57 (m, 6H).

· 3-[(1S)-1-(phenylmethylsufonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35-7.16 (m, 10H), 4.66-4.61 (m, 1H), 4.25 (m, 2H), 4.11-3.84 (m, 3H), 3.71-2.82 (m, 4H), 1.80 & 1.70 (two m, 1H), 1.28 (m, 3H), 0.85-0.58 (m, 6H).

· Methyl 3-[2-methyl-(1S)-1-(4-tert-butyloxycarbonylbutanoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.05-5.99 (two d, 1H), 4.71 (m, 1H), 3.77 (s, 3H), 3.49-3.44 (m, 1H), 2.87-2.80 (m, 1H), 2.27 (m, 4H), 2.07 (m, 1H), 1.92 (m, 2H), ~1.6 (s, 3H), 1.43 (s, 9H), 1.29 (m, 3H), 0.99-0.86 (m, 6H).

· Ethyl 3-[2-methyl-(1S)-1-(3-tert-butyloxycarbonylproanoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.20-6.15 (two d, 1H), 4.68 (m, 1H), 4.21 (m, 2H), 3.40-3.36 (m, 1H), 2.90-2.82 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.07 (m, 1H), 1.94 (m, 2H), 1.43 (s, 9H), 1.29 (m, 3H), 0.96-0.88 (m, 9H).

· Ethyl 3-[2-methyl-(1S)-1-(3-tert-butyloxycarbonylproanoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.18-6.13 (two d, 1H), 4.68 (m, 1H), 4.23 (m, 2H), 3.41-3.36 (m, 1H), 2.90-2.82 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.08 (m, 1H), 1.88 (m, 2H), 1.43 (s, 9H), 1.28 (m, 9H), 0.96-0.85 (m, 9H).

· Methyl 3-[2-methyl-(1S)-1-(3-tert-butyloxycarbonylproanoylamino)-propyl]-5-methoxymethyl-4,5-dihydro-isoxazole-5-carboxylate (diastereomeric mixture)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 6.17 (m, 1H), 4.71 (m, 1H), 3.78 (s, 3H), 3.72-3,65 (m, 2H), 3.39 (two s, 3H), 3.39-3.34 (m, 1H), 3.17-3.12 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.08 (m, 1H), 1.43 (s, 9H), 0.97-0.88 (m, 6H).

· 3-[2-methyl-(1S)-1-amino-propyl]-5-(2-naphthyl)-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (~1.3:1 diastereomers)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.99 (1H, s), 7.86-7.82 (3H, m), 7.53-7.49 (3H, m), 4.25-4.02 (3H, m), 3.55-3.48 (1H, two d, J = 7.3, 6.8Hz), 3.35 (0.45H, d, J=17.1 Hz), 3.19 (0.55H, d, J = 17.1Hz), 1.78 (1H, m), 1.22 (3H, t, J = 7.3 Hz), 0.96-0.82 (6H, m)

Example 12: Synthesis of 3-{(1S)-1- (2-naphthoylamino)-3-t-butoxycarbonyl-propyl}-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester

A solution of 3-[(1S)-1-(9-fluorenylmethyloxycarbonylamino)-3-t-butoxy-carbonyl-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carboxylic acid methyl ester (440mg, 0.842 mmol) in DMF (8.0 mL) at room temperature was treated with piperidine (2.5 mL) for 5 min. After concentration, the residue

was dissolved in DMF (10 mL), and treated with 2-naphthoic acid (174 mg, 1.2 eq), EDC (210 mg, 1.3 eq), HOBt (148 mg, 1.3 eq) and triethylamine (0.35 mL, 3.0 eq), then stirred overnight (0°C toroom temperature). Usual workup followed by chromatography gave 133 mg of the title compound and 260 mg (~50% purity) mixture.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.33 (1H, s), 7.92-7.83 (4H, m), 7.58-7.48 (2H, m), 7.34 (1H, d, J=7.8Hz), 5.04 (1H, m), 3.78 and 3.74 (3H, two s), 3.62-3.53 (1H, two d, J=17.1, 17.6Hz), 3.00-2.96 (1H, two d, J =17.1, 17.6 Hz), 2.56-2.08 (4H, m), 1.63 and 1,59 (3H, two s), 1.41 and 1.40 (9H, two s)

(E) Synthesis of aspartic acid derivatives (Examples 13 to 18)

Example 13: Synthesis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid (N-methoxy) methyl amide

A solution of N-benzyloxycarbonyl-β -t-butyl aspartic acid (2.0g, 6.2 mmol), N,O-dimethylhydroxylamine hydrochloride (724 mg, 1.2 eq) and HOBt (1.00g, 1.2 eq) in DMF (20 mL) at 0°C was treated with EDC (1.42g, 1.2 eq) and triethylamine (1.29 mL, 1.5 eq). After stirring overnight (0°C toroom temperature), the reaction was diluted with water(100mL), extracted with ethyl acetate-hexanes (1:1, 100 mL x 2), washed with water(100 mL), dried (anh Na_2SO_4), filtered and concentrated. Flash chromatography with ethyl acetate-hexanes (3:7) gave 2.039g (90%) of the title compound.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.31 (5H, m), 5.70 (1H, br), 5.16-5.08 (3H, m), 3.80 (3H, s), 3.23 (3H, s), 2.74-2.71(1H, m), 2.59 -2.57 (1H, m), 1.43 (9H, s).

Example 14: Synthesis of β -t-butyl aspartic acid N,O-dimethylhydroxyl-amine amide

Conventional hydrogenolysis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid (N-methoxy)methyl amide (H_2 balloon, 10% Pd/C, EtOH) gave the title compound (100%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 4.13 (1H, m), 3.77 (3H, s), 3.22 (3H, s), 2.71-2.67 (1H, m), 2.42-2.38 (1H, m), 1.46 (9H, s)

Example 15: Synthesis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid methyl ester

Treatment of N-benzyloxycarbonyl-β -t-butyl aspartic acid with diazomethane/ ether gave the desired methyl ester (100%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.35-7.27 (5H, m), 5.75 (1H, d), 5.13 (2H, s), 4.60 (1H, m), 3.75 (3H, m), 2.90 (1H, m), 2.76 (1H, m), 1.42 (9H, s).

Example 16: Synthesis of β -t-butyl aspartic acid methyl ester hydrochloride

Conventional hydrogenolysis of N-phenylmethyloxycarbonyl-β -t-butyl aspartic acid methyl ester (H_2 balloon, 10% Pd/C, EtOH-HCl) gave the desired product as hydrochloride salt.

Example 17: Synthesis of (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester
A solution of N-phenylmethyloxycarbonyl-β -t-butyl-aspartic acid (5.03g,

15.6 mmol), NMM (1.90 mL, 17.1 mmol) in dry THF (60 mL) under N_2 at -15°C was treated with isobutyl chloroformate (2.12 mL, 16.3 mmol) and the resulting suspension was stirred for 20 min. To the mixture at 0°C was added dry diazomethane/ether (synthesized from 2.0 eq of 1-methyl-3-nitro-1- nitroso-guanidine, 60 mL) and stirred for 30 min. When the diazo ketone synthesis was completed (TLC analysis), 30% HBr/AcOH (6.42 mL, 2.0 eq) was introduced thereto (stirred for 30-60 min.) at 0°C. The reaction was extracted with ethyl acetate, washed with sat'd $NaHCO_3$ (x 2), brine, dried (anh. Na_2SO_4), filtered and concentrated to give bromomethyl ketone derivative (6.4g).

The bromomethyl ketone(4.36g) and phenol (1.13g, 1.1 eq) in DMF (18 mL) at room temperature were treated with freshly dried KF (1.58g, 2.5 eq) and stirred for 2 h. Usual extractive workup gave crude phenoxy ketone. The crude phenoxy ketone in methanol (20 mL) at -78 °C was treated with $NaBH_4$ (412 mg) in MeOH (40 mL) (78 °C to room temperature, 2h). The reaction was quenched with acetic acid. Usual extractive workup followed by flash chromatography (ethyl acetate-hexanes = 1:5) gave 2.58g (57%) of the title compound as diastereomeric mixture. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.36-7.26 (7H, m), 6.98-6.87 (3H, m), 5.71-5.53 (NH, two d), 5.10 (2H, s), 4.24-3.92 (4H, m), 2.70-2.63 (2H, m), 1.44 and 1.43 (9H, two s).

The following compound was prepared similarly:

· (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-(1-naphthyl)oxy-pentanoic acid t-butyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.21 (1H, m), 7.80 (1H, m), 7.50-7.33 (9H, m), 6.80 (1H, m), 5.73 and 5.55 (1H, two d, J = 8.3 Hz), 5.10 (2H,

s), 4.30-4.15 (4H, m), 2.76-2.69 (2H, m), 1.44 (9H, s).

Example 18: Synthesis of (3S)-3-amino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester

Conventional hydrogenolysis of (3S)-3-phenylmethyloxycarbonylamino-4-hydroxy-5-phenoxy-pentanoic acid t-butyl ester (H_2 balloon, Pd/C, EtOH) gave the desired product (100%).
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (2H, m), 6.97-6.90 (3H, m), 4.08-3.82 (3H, m), 3.43 (1H, m), 2.63-2.37 (2H+NH_2+OH, m), 1.46 and 1.45 (9H, two s).

The following compound was prepared similarly:
· (3S)-3-amino-4-hydroxy-5-(1-naphthyl)oxy-pentanoic acid t-butyl ester
^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, m), 7.80 (1H, m), 7.50-7.34 (4H, m), 6.84 (1H, m), 4.26-4.20 (2H, m), 4.03-3.94 (1H, m), 3.51 (1H, m), 2.70-2.40 (2H, m), 1.47 and 1.46 (9H,. two s).

(F) Coupling of isoxazoline derivatives and aspartic acid derivatives and further transformations thereof (Examples 19 to 24).

Example 19: Synthesis of (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonyl-amino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide

A solution of 3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (502mg, 1.10 mmol) in THF (6.6 mL) was treated with 1N-NaOH (1.33mL). After stirring for 2.5h at room temperature, the reaction solution was quenched

with 1N-HCl (1.33 mL), then concentrated in vacuo. The residue together with sat'd NaCl(50 mL+ 2-3 mL의 1N-HCl) was extracted with ethyl acetate (100 mL x 2), dried (anh Na_2SO_4), filtered and concentrated to give 476mg (101 %) of 3-[(1S)-1-phenylmethyl-oxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid.

The crude acid (320 mg, 0.75 mmol) and β -t-butyl aspartic acid N-methyl- (N-methoxy) amide (209 mg, 1.2 eq) in DMF (5mL) at 0°C were treated with HOBt (122mg, 1.2 eq), EDC (172mg, 1.2 eq) and triethylamine (0.31 mL, 3.0 eq), and then stirred for 3h (0°C to room temperature). Concentration, conventional workup followed by flash chromatography gave less polar isomer (160mg) and more polar isomer (213mg, 33%).

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (1H, d), 7.35-7.24 (7H, m), 6.95 (1H, t, J = 7.3 Hz), 6.88 (2H, d, J = 7.8 Hz), 5.55 (1H, d), 5.18-5.08 (3H, m), 4.44 (1H, m), 4.32-4.25 (2H, m), 3.75 (3H, s), 3.32-3.25 (2H, m), 3.12 (3H, s), 2.77-2.71(1H, m), 2.62-2.56 (1H, m), 2.12 (1H, m), 1.44 (9H, s), 1.03-0.91 (6H, m).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.65 (1H, d, J = 8.3 Hz), 7.36-7.23 (7H, m), 6.95 (1H, t, J = 7.3 Hz), 6.88 (2H, d, J = 8.3 Hz), 5.19-5.11 (4H, m), 4.46 (1H, m), 4.33-4.22 (2H, ABq, J =10.3 Hz), 3.75 (3H, s), 3.33 (2H, s), 3.23 (3H, s), 2.73 (1H, m), 2.57 (1H, m), 2.07 (1H, m), 1.43 (9H, s), 1.03-0.92 (6H, m).

Example 20: Synthesis of (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonyl-amino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid t-butyl ester

The title compound was obtained from treatment of excess MeMgBr (3.0M

in ether, > 3.0 eq) to a solution of less polar isomer of (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxa-zole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide (110 mg, 0.17 mmol) in THF (5 mL) + LiCl satuated THF (2 mL) at 0°C - room temperature (44mg, 43%).

From less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.00 (1H, d, J = 9.3 Hz), 7.36-7.24 (7H, m), 6.96 (1H, t, J = 7.2 Hz), 6.87 (2H, d, J = 8.3 Hz), 5.26 (1H, d, J = 8.8 Hz), 5.12-5.09 (2H, m), 4.66 (1H, m), 4.43 (1H, d, J= 9.8 Hz), 4.21 (1H, d, J = 9.8 Hz0, 3.37-3.19 (2H, ABq, J = 18.0 Hz), 2.88 (1H, m), 2.58 (1H, m), 2.25 (3H, s), 2.03 (1H, m), 1.42 (9H, s), 0.99-0.89 (6H, m).

Similar treatment of more polar isomer of (2S)-2-{3-[(1S)-1-phenylmethyl-oxy-carbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-(N-methyl-N-methoxy) amide (135 mg) gave 52mg (41%) of the corresponding methyl ketone.

Example 21: Synthesis of (2S)-2-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

A solution of 3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenyl- methyl-4,5-dihydro-isoxazole-5-carboxylic acid (2.14g, 5.07 mmol), aspartic acid β -t-butyl ester methyl ester hydrochloride (1.46g, 1.2 eq), EDC (1.17g, 1.2 eq) and HOBt (822 mg, 1.2 eq) in DMF (19 mL) was treated with triethylamine (2.12 mL, 3.0 eq), and stirred overnight. Conventional workup followed by flash chromatography (40-50% ethyl acetate-hexanes) gave the title compound (2.94g, 94%) as a white foam.

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 and 8.25 (1H, two s), 7.96-7.79 (4H, m), 7.65-7.54 (3H, m), 7.31-7.18 (5H, m), 6.76 (0.5H, d, J = 9.3 Hz), 6.43 (0.5H, d, J = 8.8 Hz), 4.96-4.70 (2H, m), 3.71 and 3.60 (3H, two s), 3.45-3.14 (4H, m), 3.08-2.34 (2H, m), 2.15 (1H, m), 1.47 and 1.44 (9H, two s), 1.04-0.88 (6H, m).

The above compound was hydrolyzed according to the above described method (1N-NaOH in THF) to obtain the coresponding carboxylic acid (100%).

The following esters and free carboxylic acids were prepared similarly.

· (2S)-2-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.33 and 8.30 (1H, two s), 7.95-7.74 (5H, m), 7.59-7.53 (2H, m), 7.28-7.22 (2H, m), 6.99-6.89 (3.5H, m), 6.71 (0.5H, d, J = 8.8 Hz), 5.08-5.01 (1H, m), 4.83-4.79 (1H, m), 4.39-4.29 (2H, m), 3.76 and 3.64 (3H, two s), 3.44 (2H, s), 2.97-2.93 (1H, m), 2.74-2.69 (1H, m), 2.34-2.23 (1H, m), 1.45 and 1.42 (9H, two s), 1.15-1.01 (6H, m).

Hydrolysis of the above compound gave free carboxylic acid.

· (2S)-2-{3-[(1S)-1-(phenylmethyloxycarbonyl)-amino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester 1-methyl ester

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.59-7.49 (1H, m), 7.38-7.32 (5H, m), 5.25-4.95 (4H, m), 4.86 (1H, m), 4.48 (1H, m), 3.76 and 3.67 (3H, two

s), 3.29 (2H, m), 2.92 (1H, m), 2.71-2.62 (1H, m), 2.04 (1H, m), 1.48 (9H, s), 1.01-0.85 (6H, m)

· (2S)-2-{3-[(1S)-1-phenethylcarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 8.3 Hz, 0.5H), 7.47 (d, J = 9.3 Hz, 0.5 H), 7.28-7.18 (m, 10H), 5.83 & 5.44 (two d, J = 8.8 Hz, 1H), 4.70-4.52 (m, 2H), 3.68 & 3.65 (two s, 3H), 3.33-2.28 (m, 10H), 1.89 (m, 1H), 1.43 & 1.42 (two s, 9H), 0.79-0.63 (m, 6H).

· (2S)-2-{3-[(1S)-1-(1-naphthalenecarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.27 (m, 1H), 7.92-7.85 (m, 2H), 7.61-7.15 (m, 10H), 6.45 & 6.05 (two d, NH), 4.99-4.85 (m, 1H), 4.70 (m, 1H), 3.69 & 3.52 (two s, 3H), 3.50-2.32 (m, 6H), 2.12 (m, 1H), 1.40 & 1.39 (two s, 9H), 1.05-0.80 (m, 6H).

· (2S)-2-{3-[(1S)-1-(1-naphthalenesulfonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.69-8.62 (m, 1H), 8.33-7.94 (m, 3H), 7.70-7.47 (m, 3H), 7.20-7.05 (m, 5H), 5.32 & 5.15 (two m, 1H), 4.68 & 4.54 (two m, 1H), 3.85 & 3.59 (two m, 1H), 3.82 & 3.62 (two s, 3H), 3.23-1.75 (m, 7H), 1.40 & 1.34 (two s, 9H), 0.85-0.48 (m, 6H).

· (2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-

1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.53-7.49 (two d, 1H), 7.35-7.25 (m, 10H), 5.09-5.07 (m, 2.5 H), 4.88 (d, 0.5 H), 4.69 (m, 1H), 4.34 & 4.23 (two m, 1H), 3.68 &3.63 (two s, 3H), 3.36-2.23 (m, 6H), 1.89 & 1.70 (two m, 1H), 1.42 & 1.40 (two s, 9H), 0.88-0.73 (m, 6H).

· (2S)-2-{3-[(1S)-1-(indole-3-yl-ethylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.54 & 8.38 (two br s, 1H), 7.62-6.97 (m, 1H), 5.83 (d, J = 8.8 Hz, 0.5H), 5.20 (d, J = 9.3 Hz, 0.5H), 4.73-4.69 (m, 1H), 4.61 & 4.48 (two m, 1H), 3.71 & 3.59 (two s, 3H), 3.28-2.26 (m, 10H), 1.87-1.75 (m, 1H), 1.43 &1.42 (two s, 9H), 0.78-0.50 (m, 6H).

· (2S)-2-{3-[(1S)-1-(indole-3-yl-methylcarbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl-ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.37 & 8.26 (two br s, 1H), 7.54-7.12 (m, 11H), 5.95 (d, J = 8.8 Hz, 0.5H), 5.76 (d, J = 1.5 Hz, 0.5H), 4.68-4.51 (m, 2H), 3.78-3.68 (m, 2H), 3.66 & 3.62 (two s, 3H), 3.28-2.21 (m, 6H), 1.80 (m, 1H), 1.41 & 1.37 (two s, 9H), 0.75-0.46 (m, 6H).

· (2S)-2-{3-[(1S)-1-(cinnamoylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.63-7.25 (m, 12H), 6.43-6.32 (two d, J = 15.6 Hz, 1H), 6.09 & 5.68 (two d, J = 9.3 Hz, 1H), 4.78-4.70 (m, 1H), 3.69 & 3.68 (two s, 3H), 3.35-2.31 (m, 6H), 2.03 (m, 1H), 1.43 & 1.40

(two s, 9H), 0.92-0.76 (m, 6H).

· (2S)-2-{3-[(1S)-1-(phenylmethylsulfonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-succinic acid 4-t-butyl ester-1-methyl ester (diastereomeric)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.67 & 7.60 (two d, J = 8.8 Hz, 1H), 7.40-7.17 (m, 10H), 3.71 & 3.55 (two s, 3H), 3.37-2.23 (m, 6H), 1.70 (m, 1H), 1.42 & 1.47 (two s, 9H), 0.91-0.65 (m, 6H).

Example 22: Synthesis of (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester

A solution of (2S)-2-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-5-phenylmethyl-isoxazole-5-carbonyl-amino}-succinic acid 4-t-butyl ester (2.86g, 4.75 mmol) and NMM (0.57 mL, 1.1 eq) in dry THF (x mL) under N_2 at 0°C was treated with isobutyl chloroformate (0.65 mL, 1.05eq), and stirred for 20 min. To the solution at 0°C was added diazomethane, and stirred for 30 min. (TLC analysis). Additional diazomethane was needed to complete the reaction(1h). After completion of the diazoketone formation, 30% HBr/AcOH (4.0 mL, 4.0 eq) was added at 0 °C and the reaction was stirred for 1h. The reaction was extracted with ethyl acetate (x2) and the organic layer was washed with water, sat'd $NaHCO_3$ and brine, dried (anh Na_2SO_4), filtered and concentrated to give 3.36g of a yellow solid. Half of the solid (~2.375 mmol) was reacted with anhydrous KF (345 mg, 2.5 eq) and 2,6-dichlorobenzoic acid (545 mg, 1.2 eq) in DMF (10 mL) under N_2 at room temperature. Usual workup followed by flash chromatography gave the title compound as diastereomeric mixture (1.53g). Preparative HPLC (38% EtOAc/Hexane)

gave less polar diastereomer (585 mg) and more polar diastereomer (358mg).

Less polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.84-7.80 (4H, m), 7.55-7.46 93H, m), 7.29-7.24 98H, m), 6.87 (1H, d, J = 8.8 Hz), 5.05-4.93 (3H, m), 4.73 (1H, m), 3.54 (1H, d, J = 18.1 Hz), 3.34 (1H, d, J = 13.7 Hz), 3.19 (1H, d, J = 14.2 Hz), 3.11 (1H, d, J = 17.6 Hz), 2.74-2.70 (1H, m), 2.29-2.24 (2H, m), 1.39 (9H, s), 1.02 (3H, d, J = 6.4 Hz), 0.92 (3H, d, J = 6.8 Hz).

More polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.28 (1H, s), 7.97-7.75 (5H, m), 7.62-7.57 (2H, m), 7.37-7.22 (8H, m), 6.56 (1H, d, J = 8.3 Hz), 4.94 (1H, m), 4.78 (1H, m), 4.51-4.42 (2H, m), 3.51-3.43 (2H, m), 3.24-3.15 (2H, m), 2.99-2.95 (1H, m), 2.56-2.52 (1H, m), 2.18 (1H, m), 1.45 (9H, s), 1.02 (3H, d, J = 6.8 Hz), 0.97 (3H, d, J = 6.4 Hz).

The following compounds were prepared similarly.

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester

Less polar diastereomer : ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.85-7.81 (5H, m), 7.54-7.46 (2H, m), 7.31-7.23 (5H, m), 6.98-6.87 (4H, m), 5.13-5.03 (3H, m), 4.90 (1H, m), 4.39-4.27 (2H, ABq, J = 9.3 Hz), 3.51 (1H, d, J = 17.6 Hz), 3.41 (1H, d, J = 17.6 Hz), 2.94-2.78 (2H, m), 2.38 (1H, m), 1.41 99H, s), 1.12-1.08 (6H, two d, J = 6.4 Hz).

More polar diastereomer : ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H, s), 8.11 (1H, d, J = 8.8 Hz), 7.93-7.83 (4H, m), 7.59-7.53 (2H, m), 7.33-7.22 (5H, m), 6.97-6.91 (3H, m), 6.77 (1H, d, J = 8.8 Hz), 5.37 (1H, d, J = 17.1 Hz), 5.16 (1H, d, J = 17.1 Hz), 5.01-4.95 (2H, m), 4.53 (1H, d, J = 9.8 Hz), 4.25 (1H, d, J = 9.8 Hz), 3.50 (1H, d, J = 7.6 Hz), 3.32 (1H, d,

J = 7.6 Hz), 3.04-3.00 (1H, dd, J = 17.1, 4.9 Hz), 2.73-7.68 (1H, dd, 17.1, 5.4 Hz), 2.24 (1H, m), 1.47 (9H, s), 1.10-1.03 (6H, two d, J = 6.4 Hz).

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid-t-butyl ester (diastereomeric mixture)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.72-7.60 (1H, m), 7.37-7.30 (8H, m), 5.40 (0.5H, d), 5.23-4.85 (6.5H, m), 4.40 (1H, m), 3.30 (2H, m), 2.92-2.65 (2H, m), 2.10-1.98 (1H, m), 1.44 (9H, s), 1.00-0.87 (6H, m).

Following compounds were similarly prepared:

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 8.7 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.88 9d, J = 7.8 Hz, 1H), 7.78 (m, 1H), 7.63 (m, 1H), 7.22-7.15 (m, 4H), 6.96-6.81 (m, 6H), 4.99-4.81 (m, 4H), 4.40 (d, J = 10.1 Hz, 1H), 4.21 (d, J = 10.0 Hz, 1H), 3.44 (d, J = 17.9 Hz, 1H), 3.24 (d, J = 17.9 Hz, 1H), 3.03 (dd, J = 17.0, 4.6 Hz, 1H), 2.76 (dd, J = 17.0, 5.5 Hz, 1H), 2.30(m, 1H), 1.45 (s, 9H), 1.10 (m, 6H)

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.68 (d, J = 8.7 Hz, 1H), 8.32-8.26 (m, 2H), 8.17 (d, J = 8.7 Hz, 1H), 7.91 (m, 2H), 7.80 (m, 1H), 7.66 (m, 1H), 7.28 (m, 4H), 7.02-6.87 (m, 6H), 5.01-4.77 (m, 4H), 4.38-4.30 (m, 2H), 3.50-3.38 (ABq, J = 17.9 Hz, 2H), 3.06-3.02 (m, 1H), 2.84-2.80 (m, 1H), 2.34 (m, 1H), 1.44 (s, 9H), 1.14 (m, 6H)

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenoxymethy-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid.

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.01 (d, J = 9.2 Hz, 1H), 8.87 (d, J = 8.3 Hz, 1H), 8.55 (d, J = 8.3 Hz, 1H), 8.18-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.28-7.14 (m, 4H), 6.96-6.75 (m, 6H), 5.00-4.75 (m, 4H), 4.42 (d, J = 10.6 Hz, 1H), 4.22 (d, J = 10.6 Hz, 1H), 3.47-3.35 (ABq, J = 17.9 Hz, 2H), 2.82 (dd, J = 17.0, 6.4 Hz, 2.56 (m, 1H), 2.33 (m, 1H), 0.98 (m, 6H).

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.06 (d, J = 9.2 Hz, 1H), 8.88 (d, J = 7.8 Hz, 1H), 8.57 (d, J = 8.7 Hz, 1H), 8.22-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.17 (m, 4H), 6.91-6.78 (m, 6H), 4.98-4.90 (ABq, J = 17.9 Hz, 2H), 4.77 (m, 2H), 4.35 (d, J = 10.6 Hz, 1H), 4.20 (d, J = 10.6 Hz, 1H), 3.47-3.35 (ABq, J = 18.3 Hz, 2H), 2.89 (dd, J = 17.0, 6.4 Hz, 2.61 (dd, J =17.0, 6.4, 1H), 2.31 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.3 Hz), 7.94 (d, J = 8.3 Hz), 7.88 (d, J = 7.4 Hz, 1H), 7.74 (d, J = 9.7 Hz, 1H), 7.61-7.44 (m, 4H), 7.35-7.18 (m, 8H), 6.23 (d, J = 8.7 Hz, 1H), 4.95 (m, 1H), 4.76 (m, 1H), 4.49-4.41 (ABq, J = 17.5 Hz, 2H), 3.49-3.41 (m, 2H), 3.22-3.12 (m, 2H), 2.92 (dd, J = 17.0, 4.2 Hz, 1H), 2.52 (dd, J = 17.0, 5.1 Hz, 1H), 2.13 (m, 1H), 1.37 (s, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.3 Hz,

1H), 7.83 (m, 2H), 7.57-7.47 (m, 4H), 7.38-7.22 (m, 9H), 6.64 (d, J = 9.2 Hz, 1H), 5.00-4.87 (m, 3H), 4.72 (m, 1H), 3.60 (d, J = 17.9 Hz, 1H), 3.36 (d, J = 14.2 Hz, 1H), 3.20 (d, J = 14.2 Hz, 1H), 3.12 (d, J = 17.9 Hz, 1H), 2.69 (dd, J = 17.0, 4.6 Hz, 1H), 2.28-2.18 (m, 2H), 1.38 (s, 9H), 1.06 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester (more polar isomer)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 1H), 7.62 (d, J = 15.6 Hz, 1H), 7.50 (m, 1H), 7.38-7.21 (m, 12H), 6.39 (d, J = 15.6 Hz, 1H), 5.90 (d, J = 9.2 Hz, 1H), 4.76 (m. 2H), 4.49-4.41 (ABq, J = 17.4 Hz, 2H), 3.42-3.38 (m, 2H), 3.17 (d, J = 14.2 Hz, 1H), 3.09 (d, J = 17.9 Hz, 1H), 2.91 (dd, J = 17.4, 4.6 Hz, 1H), 2.52 (dd, J = 17.4, 5.0 Hz, 1H), 2.04 (m, 1H), 1.41 (s, 9H), 0.90 (m, 6H).

Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.61 (d, 1H), 7.52 (d, 1H), 7.41 (d, 1H), 7.28 (m, 12H), 6.64-6.41 (m, 2H), 5.09-4.99 (ABq, J = 17.4 Hz, 2H), 4.81 (m, 1H), 4.69 (m, 1H), 3.50 (d, J = 17.9 Hz, 1H), 3.34 (d, J = 14.2 Hz, 1H), 3.17 (d, J = 14.2 Hz, 1H), 3.04 (d, J = 17.9 Hz, 1H), 2.74 (dd, J = 17.0, 4.2 Hz, 1H), 2.22 (m, 2H), 1.39 (s, 9H), 0.97-0.88 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester

More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 9.3 Hz, 1H), 7.38-7.23 (m, 13H), 4.80-4.63 (m, 2H), 4.56-4.46 (ABq, J = 17.1 Hz, 2H), 4.21-4.10 (m, 2H), 3.83 (m, 2H), 3.41-3.37 (m, 1H), 3.19 (d, J = 14.2 Hz, 1H), 2.90-2.83 (m, 2H), 2.53 (m, 1H), 1.76 (m, 1H), 1.41 (s,

9H), 0.83 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H).
Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 9.2 Hz, 1H), 7.36-7.26 (m, 13H), 5.05-4.95 (m, 3H), 4.74 (m, 1H), 4.17 (m, 2H), 3.96 (m, 1H), 3.41-2.99 (m, 4H), 2.70 (m, 1H), 2.19 (m, 1H), 1.79 (m, 1H), 1.39 (s, 9H), 0.86 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.8 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester
More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 8.7 hz, 1H), 8.31 (d, J = 8.7 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.78-7.72 (m, 2H), 7.62 (m, 1H), 7.33-7.27 (m, 3H), 5.20-5.05 (m, 3H), 4.92-4.89 (m, 2H), 3.47-3.34 (m, 2H), 2.95 (dd, J = 17.0, 4.6 Hz, 1H), 2.73 (dd, J = 17.0, 5.1 Hz, 1H), 2.28 (m, 1H), 1.45 (s, 9H), 1.07 (m, 6H).
Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 9.2 Hz, 1H), 8.28-8.24 (m, 2H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75-7.59 (m, 3H), 7.31-7.25 (m, 3H), 5.12-4.89 (m, 5H), 3.46-3.41 (m, 2H), 2.92 (dd, J = 17.0, 5.1 Hz, 1H), 2.78 (dd, J = 17.0, 5.5 Hz, 1H), 2.30 (m, 1H), 1.44 (s, 9H), 1.10 (m, 6H)

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid t-butyl ester
More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 9.2 Hz, 1H), 8.32 9d, J = 8.3 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.80-7.63 (m, 3H), 7.36-7.18 (m, 8H), 4.82 (m, 1H), 4.72 (m, 1H), 4.47-4.37 (ABq, J = 17.0 Hz, 2H), 3.47 (d, J = 17.9 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.19 (d, J = 14.2 Hz,

1H), 3.14 (d, J = 17.9 Hz, 1H), 2.94 (dd, J = 17.4, 4.1 Hz, 1H), 2.53 (dd, J = 17.0, 5.0 Hz, 1H), 2.18 (m, 1H), 1.45 (s, 9H), 0.98 (m, 6H).
Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.52 (d, J = 9.2 Hz, 1H), 8.28-8.23 (m, 2H), 8.12 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 7.73 (m, 1H), 7.62-7.55 (m, 2H), 7.31-7.17 (m, 8H), 5.06-4.98 (ABq, J = 17.0 Hz, 2H), 4.84 (m, 1H), 4.69 (m, 1H), 5.54 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 14.2 H, 1H), 3.16 (d, J = 14.2 Hz, 1H), 3.10 (d, J = 17.9 Hz, 1H), 2.70 (dd, J = 17.0, 4.1 Hz, 1H), 2.21 (m, 1H), 2.11 (dd, J = 17.0, 5.1 Hz, 1H), 1.38 (s, 9H), 0.98 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester
More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.47 (d, J = 9.2 Hz, 1H), 8.32 (d, J = 8.7 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.78 (m, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.64 (t, J = 7.3 Hz, 1H), 7.29-7.17 (m, 4H), 7.06 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 8.3 Hz, 2H), 4.81-4.72 (m, 2H), 4.47-4.28 (ABq, J = 17.9 Hz, 2H), 3.42 (d, J = 17.9 Hz, 1H), 3.34 (d, J = 14.2 Hz, 1H), 3.15 (d, J = 13.7 Hz, 1H), 3.10 (d, J = 17.9 Hz, 1H), 2.94 (dd, J = 17.4, 4.1 Hz, 1H), 2.64 (dd, J = 17.4, 5.5 Hz, 1H), 2.15 (m, 1H), 1.43 (s, 9H), 0.95 (m, 6H).
Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.50 (d, J = 9.2 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.74 (m, 1H), 7.62-7.56 (m, 2H), 7.29-7.16 (m, 5H), 6.88 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.8 Hz, 2H), 4.81-4.66 (m, 4H), 3.46 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 13.8 Hz, 1H), 3.15 (d, J = 13.8 Hz, 1H), 3.07 (d, J = 17.9 Hz, 1H), 2.76 (dd, J = 17.0, 4.1 Hz, 1H), 2.21-2.09 (m, 2H), 1.37 (s, 9H), 0.93 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid t-butyl ester

Diastereomeric mixture: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (m, 1H), 7.96-7.50 (m, 7H), 6.85-6.73 (m, 1H), 5.10-4.97 (m, 2H), 4.66 (m, 1H), 3.40 (m, 2H), 2.94-2.60 (m, 2H), 2.32-2.14 (m, 1H), 2.22 & 2.10 (two s, 3H), 1.43 & 1.42 (two s, 9H), 1.10-0.95 (m, 6H).

Example 23: Synthesis of (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonyl-amino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester

The title compound was prepared with conventional EDC coupling of 3-[2-methyl-(1S)-1-(naphthalene-2-car-bonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carboxylic acid (1.00g, 2.24 mmol) and (3S)-3-amino- 4-hydroxy-5- phenoxy-pentanoic acid t-butyl ester (630 mg, 1.0 eq), EDC (558 mg, 1.3 eq), HOBt(394 mg, 1.3 eq) and triethylamine (0.94 mL, 3.0 eq) in DMF (5 mL). Usual workup followed by flash chromatography gave 1.44g of coupled product. The coupled product and Dess-Martin reagent (2.15g, 2.5 mol eq) in dry CH_2Cl_2 (25mL) under N_2 at room temperature was stirred for 1h, then quenched with isopropyl alcohol(3 mL). Usual extractive workup followed by flash chromatography (36% ethyl acetate-hexane) gave 1.27g of the title compound as diastereomeric mixture. Preparative HPLC (36% ethyl acetate-hexanes, 10 mL/min, 278 nm UV detection) afforded less polar (352 mg) and more polar (536 mg) diastereomers.

Less polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.93-7.81 (5H, m), 7.58-7.51 (2H, m), 7.28-7.21 94H, m), 6.99-6.76 (7H, m), 5.00-4.98 (2H, m), 4.79-4.66 (2H, ABq, J = 16.6 Hz), 4.35-4.29 (2H,

ABq, J = 10.3 Hz), 3.40 (2H, s), 3.02-2.98 (1H, dd, J = 16.6, 4.9 Hz), 2.84-2.79 (1H, dd, J = 16.6, 4.7 Hz), 2.30 (1H, m), 1.41 (9H, s), 1.12-1.07 (6H, two d, J = 6.8 Hz).

More polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 7.99-7.82 (5H, m), 7.59-7.53 (2H, m), 7.26-7.18 (4H, m), 6.97-6.83 (6H, m), 6.68 (1H, d, J = 8.3 Hz), 5.01-4.95 (3H, m), 4.83 (1H, d, J = 17.1 Hz), 4.42 (1H, d, J = 9.8 Hz), 4.23 (1H, d, J = 9.8 Hz), 3.49-3.32 (2H, ABq, J = 18.1 Hz), 3.06-3.02 (1H, dd, J = 17.1, 4.4 Hz), 2.76-2.72 (1H, dd, J = 17.1, 5.4 Hz), 2.24 (1H, m), 1.45 (9H, s), 1.10-1.02 (6H, two d, J = 6.8 Hz).

The following compounds were prepared similarly:

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-2-carbonylamino)-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-5-(2-naphthyloxy)-pentanoic acid-t-butyl ester

Less polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.27(1H, s), 7.89 (8H, m), 7.56-7.26 (6H, m), 7.23-6.87 (5H, m), 6.74 (1H, d, J = 9.3 Hz), 5.04-4.95 (2H, m), 4.92-4.80 (2H, ABq, J = 16.6 Hz), 4.37-4.30 (2H, ABq, J = 23.4, 10.3 Hz), 3.43-3.38 (2H, ABq, J = 22.5, 17.8 Hz), 3.05-3.00 (1H, dd, J = 16.6, 4.9 Hz), 2.86-2.82 (1H, dd, J = 16.6, 4.9 Hz), 2.25 (1H, m), 1.42 (9H, s), 1.09-1.05 (6H, two d, J = 6.8, 6.7 Hz).

More polar diastereomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.30 (1H, s), 8.02-7.55 (10H, m), 7.41-7.05 (6H, m), 6.89-6.66 (4H, m), 5.10-4.94 (4H, m), 4.41 (1H, d, J = 9.8 Hz), 4.23 91H, d, J = 10.3 Hz), 3.50-3.34 (2H, ABq, J = 17.6 Hz), 3.09-3.05 (1H, dd, J = 17.1, 4.4 Hz), 2.79-2.74 (1H, dd, J = 17.1, 5.4 Hz), 2.25 (1H, m), 1.45 (9H, s), 1.10-1.02 (6H, two d, J = 6.8 Hz).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid t-butyl ester
More polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J = 9.2 Hz, 1H), 8.32-8.25 (m, 2H), 8.13 (d, J = 8.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.79-7.62 (m, 3H), 7.27 (m, 2H), 6.97 (m, 1H), 6.88 (m, 2H), 5.04-4.72 (m, 5H), 3.48-3.34 (m, 2H), 3.00 (dd, J = 17.0, 4.6 Hz, 1H), 2.77 (dd, J = 17.0, 5.5 Hz, 1H), 2.27 (m, 1H), 1.45 (s, 9H), 1.06 (m, 6H).
Less polar isomer: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.58 (d, J = 9.2 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.78-7.59 (m, 3H), 7.22 (m, 2H), 6.92 (m, 1H), 6.82 (m, 2H), 5.04-4.88 (m, 3H), 4.82-4.69 (ABq, J = 17.0 Hz, 2H), 3.45-3.33 (m,2H), 2.99 (dd, J = 16.5, 4.6 Hz, 1H), 2.78 (dd, J = 16.5, 5.1 Hz, 1H), 2.26 (m, 1H), 1.42 (s, 9H), 1.06 (m, 6H)

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 89LP precursor)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.7 Hz, 1H), 7.32 (m, 3H), 6.42 (m, 1H), 5.20-5.05 (ABq, J = 17.0 Hz, 2H), 4.90 (m, 1H) 4.67 (m, 1H), 3.38 (d, J = 17.9 Hz, 1H), 2.92 (m, 2H), 2.78 (m, 1H), 2.53 (m, 2H), 2.40 (m, 2H), 2.18 (m, 1H), 2.03 (m, 1H), 1.79 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 1.26 (m, 6H), 0.94 (m, 6H), 0.86 (t, J = 6.9 Hz, 3H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; more polar isomer (Compound 90MP precursor)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.7 Hz, 1H), 7.31 (m, 3H), 6.17 (d, J = 8.7 Hz, 1H), 5.17-5.07 (ABq, J = 17.0 Hz, 2H), 4.87 (m,

1H) 4.65 (m, 1H), 3.30 (d, J = 17.9 Hz, 1H), 2.96-2.90 (m, 2H), 2.69 (m, 1H), 2.56 (m, 2H), 2.45 (m, 2H), 2.03 (m, 2H), 1.81 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H), 1.26 (m, 6H), 0.94-0.86 (m, 9H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 85LP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 9.2 Hz, 1H), 7.34-7.22 (m, 8H), 6.37 (d, J = 9.2 Hz, 1H), 5.10-4.98 (ABq, J = 17.4 Hz, 2H), 4.70 (m, 1H) 4.61 (m, 1H), 3.46 (d, J = 17.9 Hz, 1H), 3.31 (d, J = 14.2 Hz, 1H), 3.14 (d, J = 14.2 Hz, 1H), 2.99 (d, J = 17.9 Hz, 1H), 2.73 (m, 1H), 2.53 (m, 2H), 2.40 (m, 2H), 2.18 (m, 1H), 2.09 (m, 1H), 1.42 (s, 9H), 1.39 (s, 9H), 0.90 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 91LP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 8.7 Hz, 1H), 7.32 (m, 3H), 6.42 (d, J = 9.2, 1H), 5.21-5.05 (ABq, J = 17.0 Hz, 2H), 4.91 (m, 1H) 4.67 (m, 1H), 3.37 (d, J = 17.9 Hz, 1H), 2.94 (m, 2H), 2.79 (m, 1H), 2.53 (m, 2H), 2.40 (m, 2H), 2.18 (m, 1H), 2.07 (m, 1H), 1.86 (m, 1H), 1.43 (s, 9H), 1.41 (s, 9H), 0.94 (m, 9H).

· t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; less polar isomer (Compound 73LP precursor)

^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.7 Hz, 1H), 7.32 (m, 3H),

6.44 (d, J = 9.2, 1H), 5.20-5.04 (ABq, J = 17.0 Hz, 2H), 4.88 (m, 1H) 4.67 (m, 1H), 3.46 (d, J = 17.9 Hz, 1H), 2.94-2.76 (m, 3H), 2.53 (m, 2H), 2.40 (m, 2H), 2.19 (m, 1H), 1.62 (s, 3H), 1.43 (s, 9H), 1.41 (s, 9H), 0.95 (m, 6H).

t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlor obenzoyloxy)-pentanoate; more polar isomer (compound 74MP precursor)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.7 Hz, 1H), 7.33 (m, 3H), 6.18 (d, J = 8.7 Hz, 1H), 5.18-5.05 (ABq, J = 16.5 Hz, 2H), 4.87 (m, 1H) 4.65 (m, 1H), 3.38 (d, J = 17.9 Hz, 1H), 2.93-2.89 (m, 2H), 2.71 (m, 1H), 2.57 (m, 2H), 2.46 (m, 2H), 2.02 (m, 1H), 1.66 (s, 3H), 1.58 (s, 9H), 1.46 (s, 9H), 0.95-0.86 (m, 6H).

t-Butyl (3S)-3-{3-[2-methyl-(1S)-1-(3-t-butyloxycarbonylpropanoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoate; more polar isomer (Compound 86MP precursor)
^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 9.2 Hz, 1H), 7.30 (m, 8H), 6.07 (d, J = 8.7 Hz, 1H), 4.72 (m, 1H), 4.60 (m, 1H), 4.45-4.36 (ABq, J = 17.0 Hz, 2H), 3.40-3.32 (m, 2H), 3.17 (d, J = 14.2 Hz, 1H), 3.06 (d, J = 17.9 Hz, 1H), 2.93 (m, 1H), 2.60-2.38 (m, 5H), 1.98 (m, 1H), 1.44 (s, 9H), 1.41 (s, 9H), 0.88-0.82 (m, 6H).

Example 24: Synthesis of (3S)-3-{3-[(1S)-1-benzyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid

A solution of (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-

propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid t-butyl ester (less polar diastereomer) (44mg) in CH_2Cl_2 (2 mL) at 0°C was treated with TFA (1 mL). The reaction mixture was stirred for 2h while slowly warming to room temperature. Concentration gave the title compound (compound 10, quantitative)

^1H NMR (500 MHz, CD_3OD) δ 7.35-6.90 (10H, m), 5.11 (2H, s), 4.53 (1H, m), 4.47 (1H, m), 4.23 (2H, dd), 2.86 (1H, dd), 2.54 (1H, dd), 2.24 (3H, s), 2.00 (1H, m), 1.00 and 0.97 (6H, two d); MS $[M+Na]^+$ 562

The following compound was prepared similarly from the less polar isomer:

· (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid (compound 11).

^1H NMR (500 MHz,) δ 8.76 (1H,d, J = 7.8 Hz), 7.76 (1H, d, J = 8.8 Hz), 7.36-6.87 (10H, m), 5.06 (2H, m), 4.50 (1H, m), 4.32 (1H, m), 4.16 (2H, m), 3.21 (2H, app s), 2.79 (1H, m), 2.06 (3H, s), 1.89 (1H, m), 0.91 (3H, d, J = 6.3 Hz), 0.80 (3H, d, J = 6.3 Hz).

The following final compounds were obtained by a similar TFA deprotection of the corresponding t-butyl ester.

· (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 3, diastereomeric mixture)

^1H NMR (500 MHz, DMSO-d_6) δ 8. 49 (1H, m), 7.72 (1H, m), 7.35 (5H, m), 5.03 (3H, m), 4.40 (1H, m), 4.15 (1H, m), 3.24 (2H, m), 2.54 (2H, m), 2.04 and 1.95 (3H, wo s), 1.88 (1H, m), 0.90-0.81 (6H, m): MS $[M+Na]^+$ 456

· (3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 14, diastereomeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (1H, br s), 7.75 (1H, m), 7.61-7.30 (8H, m), 5.30-5.00 (5H, m), 4.70 (1H, m), 4.16 (1H, m), 2.66 (2H, m), 1.90 (1H, m), 0.95-0.79 (6H, m): MS $[M+Na]^+$ 644

· (3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 17, diastereomeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.92-8.55 (2H, m), 8.15-7.98 (3H, m), 7.63-7.55 (4H, m), 7.25-7.15 (4H, m), 6.95-6.74 (6H, m), 5.20-4.15 (6H, m), 2.80-2.55 (2H, m), 2.05 (1H, m), 1.05-0.89 (6H, m): MS $[M+Na]^+$ 674.

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 18)

From less polar t-butyl ester: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (1H, d, J = 7.8 Hz), 8.79 (1H, d, J = 8.3 Hz), 8.48 (1H, s), 8.05-7.94 (4H, m), 7.64-7.58 (2H, m), 7.30-7.17 (4H, m), 6.94-6.83 (6H, m), 4.96 (2H, app s), 4.78 (1H, m), 4.73 (1H, m), 4.36 (1H, d, J = 10.2 Hz), 4.22 (1H, d, J = 10.2 Hz), 3.37 (2H, app s), 2.91 (1H, dd, J = 16.6, 6.4 Hz), 2.62 (1H, dd, J = 16.6, 5.9 Hz), 2.12 (1H, m), 1.00 (3H, d, J = 6.3 Hz), 0.87 93H, d, J = 6.3 Hz): MS $[M+Na]^+$ 674

From more polar t-butyl ester: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (1H, d, J = 8.3 Hz), 8.79 (1H, d, J = 8.8 Hz), 8.43 (1H, s), 8.00-7.80 (4H, m), 7.61 (2H, m), 7.23-7.17 94H, m), 6.93-6.77 (6H, m), 4.99 (1H,

d, J = 17.6 Hz), 4.86 (1H, d, J = 18.1 Hz), 4.79 (1H, m), 4.72 (1H, m0, 4.43 (1H, d, J = 10.7 Hz), 4.20 (1H, d, J = 10.2 Hz), 2.81 (1H, dd), 2.56 (1H, dd), 2.17 (1H, m), 1.01 (3H, d, J = 6.3 Hz), 0.99 (3H, d, J = 6.3 Hz): MS $[M+Na]^+$ 674

· (3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 27)

From less polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 9.08 (1H, d, J = 7.8 Hz), 8.87 (1H, d, J = 8.8 Hz), 8.55 (1H, s), 8.10-8.01 (4H, m), 7.68 7.58 (5H, m), 7.26 (2H, t, J = 7.8 Hz), 6.98-6.92 (3H, m), 5.27 (2H, ABq, J = 16.6 Hz0, 4.82-4.78 (2H, m), 4.43 (1H, d, J = 10.7 Hz), 4.29 (1H, d, J = 10. 3 Hz), 3.44 (2H, ABq, J = 18.1 Hz), 3.01 (1H, dd, J = 17.1, 6.4 Hz), 2.67 (1H, dd, J = 17.1, 6.3 Hz), 2.21 (1H, m), 1.07 (3H, d, J = 6.2 Hz), 0.97 (3H, d, J = 6.2 Hz): MS $[M+Na]^+$ 770

From more polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 8.97 (1H, d, J = 7.8 Hz), 8.85 (1H, d, J = 8.3 hz), 8.50 (1H, s), 8.09-7.96 (4H, m), 7.67-7.60 (5H, m), 7.32 (2H, t, J = 6.3 Hz), 7.00 (3H, m), 5.38 (1H, d, J = 17.1 Hz), 5.13 (1H, d, J = 17.1 Hz), 4.92 (1H, d, J = 6.3 Hz), 4.79 (1H, t, J = 7.8 Hz), 4.55 (1H, d, J = 9.7 Hz), 4.28 (1H, d, J = 8.7 Hz), 3.48 (1H, d, J = 18.1 Hz), 3.38 (1H, d, J = 18.1 Hz), 2.87 (1H, dd, J = 17.1, 4.9 Hz), 2.60 (1H, dd, J = 17.1, 4.9 Hz), 2.25 (1H, m), 1.07 (6H, m): MS $[M+Na]^+$ 770

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 23, diastereomeric)

^1H NMR (500 MHz, DMSO-d_6) δ 8.72-8.55 (2H, m), 8.38 (1H, s), 8.04-7.85 (4H, m), 7.62 (2H, m), 7.25-7.12 (7H, m), 6.91-6.70 (3H, m),

4.79-4.51 (4H, m), 3.40-3.05 (4H, m), 2.73-2.23 (2H, m), 2.01 (1H, m), 0.94-0.70 (6H, m): MS $[M+Na]^+$ 658

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid (compound 28)

From less polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 8.68 (1H, d, J = 8.8 Hz), 8.59 (1H, d, J = 8.3 Hz), 8.40 (1H, s), 8.05-7.87 (4H, m), 7.63-7.54 (5H, m), 7.21-7.13 (5H, m), 5.98 (2H, ABq, J = 17.1 Hz), 4.74 (1H, m), 4.64 (1H, m), 3.25-3.10 (4H, m), 2.62 (1H, dd, J = 17.1, 6.3 Hz), 2.37 (1H, dd, J = 16.6, 5.4 Hz), 2.06 (1H, m), 0.93 (3H, d, J = 6.8 Hz), 0.83 (3H, d, J = 6.2 Hz): MS $[M+Na]^+$ 754

From more polar t-butyl ester: ^1H NMR (500 MHz, DMSO-d_6) δ 8.72 (1H, d, J = 8.3 Hz), 8.59 91H, d, J = 8.8 Hz), 8.41 (1H, s), 8.01-7.87 (4H, m), 7.62-7.53 (5H, m), 7.29-7.21 (5H, m), 4.70-4.55 (4H, m), 3.44-3.10 (4H, m), 2.72-2.67 (1H, dd, J = 16.6, 7.3 Hz), 2.38-2.34 (1H, dd, J = 16.6, 7.3 Hz), 2.05 (1H, m), 0.97 (3H, d, J = 6.3 Hz), 0.79 (3H, d, J = 6.3 Hz); MS $[M+Na]^+$ 754.

· (3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenox ymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 22, diastereomeric mixture)

^1H NMR (500 MHz, DMSO-d_6) δ 9.06 (1H, m), 8.82 91H, br), 8.57 (1H, m), 8.16-7.74 95H, m), 7.26-7.12 (4H, m), 6.89-6.69 (6H, m), 5.10-4.70 (4H, m), 4.48-4.20 (2H, m), 2.87-2.53 (2H, m), 2.32 (1H, m), 0.98-0.85 (6H, m): MS $[M+Na]^+$ 675, $[M+H]^+$ 653.

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenox ymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pent

anoic acid (compound 25)

From less polar t-butyl ester: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (1H, d, J = 7.8 Hz), 8.77 (1H, d, J = 8.3 Hz), 8.47 (1H, s), 8.03-7.57 (9H, m), 7.44 (1H, t, J = 6.8 Hz), 7.34 (1H, t, J = 7.8 Hz), 7.17-7.13 (4H, m), 6.88-6.82 (3H, m), 5.09 (2H, ABq), 4.84 (1H, m), 4.72 (1H, m), 4.38 (1H, d, J = 10.2 Hz), 4.23 (1H, d, J = 10.7 Hz), 2.94 (1H, dd, J = 17.1, 6.8 Hz), 2.65 (1H, dd, J = 16.6, 5.9 Hz), 2.12 (1H, m), 0.97 (3H, d, J = 6.3 Hz), 0.85 (3H, d, J = 6.3 Hz): MS $[M+Na]^+$ 724

From more polar t-butyl ester: ^{1}H NMR (50°C, 300 MHz, DMSO-d_6) δ 8.72 (1H, d), 8.63 (1H, d), 8.41 (1H, s), 7.94-6.72 (19H, m), 5.03 (2H, ABq), 4.88 (1H, m), 4.74 (1H, m), 4.42 91H, d), 4.19 (1H, m), 3.38 (2H, ABq), 2.88 (1H, dd), 2.65 (1H, dd), 2.19 (1H, m), 1.02 (6H, two d):MS $[M+Na]^+$ 724

^{13}C NMR (50°C, 300 MHz, DMSO-d_6) δ 202.1, 171.6, 170.7, 166.6, 159.3, 158.0, 155.6, 134.1, 133.9, 132.0, 131.6, 129.3, 129.1, 128.7, 127.7, 127.5, 127.3, 126.5, 126.2, 124.2, 123.6, 121.1, 118.1, 114.5, 107.4, 87.5, 70.2, 52.9, 34.4, 29.6, 19.4, 18.9.

More polar diastereomer's methyl ester: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (1H, s), 8.02-6.68 (20H, m), 5.09-4.95 (2H, ABq, J = 16.6 Hz), 5.10 (1H, m), 5.01(1H, m), 4.34 (2H, ABq, J = 10.3 Hz), 3.70 (3H, s), 3.50-3.33 (2H, ABq, J = 17.6 Hz), 3.13 (1H, dd, J = 17.1, 4.9 Hz), 2.90 (1H, dd, J = 17.1, 5.9 Hz), 2.23 (1H, m), 1.08 and 1.02 (6H, two d, J = 6.8 Hz).

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid (compound 24, diasteromeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.02-8.18(3H, m), 8.05-6.80 (18H, m), 5.15-4.15 (6H, m), 2.90-2.55 (2H, m), 2.14 (1H, m), 1.05-0.82 (6H, m).

· (3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid (compound 29, diasteromeric mixture)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95-8.46 (3H, m), 8.09-7.07 (13H, m), 5.21-4.75 (5H, m), 2.95-2.64 (2H, m), 2.19 (1H, m): MS $[M+H]^+$ 596

· (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 30, diasteromeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.76-8.69 (m, 2H), 8.45 (m, 1H), 8.04-7.90 (m, 5H), 7.61 (m, 2H), 7.31-7.19 (m, 2H), 6.97-6.81 (m, 3H), 5.09-4.68 (m, 5H), ~3.3 (m, 2H), 2.82 (m, 1H), 2.64 (m, 1H), 2.15 ((m, 1H), 1.00-0.84 (m, 6H): MS [M+Na] = 568

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 32, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.48 (br s, 1H), 8.00 (m, 1H), 7.61-7.54 (m, 3H), 7.30-7.15 (m, 11H), 4.93-4.32 (m, 4H), 3.34-2.90 (m, 4H), 2.78 (m, 1H), 1.78 (m, 1H), 0.90-0.60 (m, 6H): MS [M+Na] = 732

· (3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(compound 33)

From more polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.80 (d, J = 8.3 Hz, 1H), 8.63 (d, J = 7.8 Hz, 1H), 8.02 (m, 3H), 7.64-7.20 (m, 12H), 4.81-4.55 (m, 4H), 3.39 (m, 2H), 3.12 (m, 2H), 2.73 (m, 1H),

2.43 (m, 1H), 1.98 (m, 1H), 0.99 (d, J = 4.6 Hz, 3H), 0.79 (d, J = 4.5 Hz, 3H): MS [M+Na] = 754

From less polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 8.7 Hz, 1H), 8.62 (d, J = 8.3 Hz, 1H), 8.08-7.97 (m, 4H), 7.61-7.21 (m, 12H), 5.00 (m, 2H), 4.77-4.67 (m, 2H), 3.39-3.27 (m, 2H), 3.15-3.11 (m, 2H), 2.64 (m, 1H), 2.40 (m, 1H), 1.99 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 38)

Fom more polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.55 (d, J = 8.7 Hz, 1H), 8.28 (d, J = 8.7 Hz, 1H), 7.60-7.19 (m, 14H), 6.70 (d, J = 15.6 Hz, 1H), 4.71-4.49 (m, 4H), ~3.3 (m, 2H), 3.08 (m, 2H), 2.71 (m, 1H), 2.40 (m, 1H), 1.90 (m, 1H), 0.86 (d, J = 6.4 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H): MS [M+H] = 708

From less polar t-butyl ester: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.53 (d, J = 8.3 Hz, 1H), 8.28 (d, J = 8.7 Hz, 1H), 7.61-7.16 (m, 14H), 6.69 (d, J = 16.9 Hz, 1H), 4.99-4.92 (ABq, J = 17.4 Hz, 2H), 4.72 (m, 1H), 4.53 (m, 1H), 3.36 (d, J = 17.9 Hz, 1H), 3.23 (d, J = 13.8 Hz, 1H), 3.10-3.04 (m, 2H), 2.61 (dd, J = 17.0, 6.4 Hz, 1H), 2.37 (dd, J = 17.0, 6.0 Hz, 1H), 1.90 (m, 1H), 0.79 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 39, diastereomeric)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 7.75 and 7.69 (m, 1H), 7.61-7.13 (m, 13H), 5.00 and 4.70 (m, 1H), 4.64 (m, 2H), 4.22-3.78 (m, 4H), 1.79 (m, 1H), 0.90 (m, 6H):MS [M+H] = 732.

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (compound 40)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.94 (d, J = 9.7 Hz, 1H), 8.75 (d, J = 7.8 Hz, 1H), 8.55 (d, J = 8.8 Hz, 1H), 8.18-8.05 (m, 3H), 7.85 (m, 1H), 7.55 (m, 3H), 5.22-5.06 (m, 3H), 4.83-4.70 (m, 2H), 3.35 (m, 2H), 2.80 (m, 1H), 2.61 (m, 1H), 2.31 (m, 1H), 0.95 (m, 6H):MS [M+H] = 643

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.07 (d, J = 9.2 Hz, 1H), 8.76 (d, J = 8.3 Hz, 1H), 8.56 (d, J = 8.7 Hz, 1H), 8.20-8.07 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.62-7.54 (m, 3H), 5.21-5.06 (m, 3H), 4.84-4.70 (m, 2H), 3.44-3.27 (m, 2H), 2.85 (dd, J = 17.0, 6.0, 1H), 2.66 (dd, J = 17.0, 6.9 Hz, 1H), 2.29 (m, 1H), 0.98 (d, J = 6.9 Hz, 3H), 0.90 (d, J = 6.4 Hz, 6H)

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 41)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.95 (d, 1H), 8.72 (d, 1H), 8.55 (d, 1H), 8.20-8.05 (m, 3H), 7.86 (m, 1H), 7.72 (m, 1H), 7.24-6.74 (m, 5H), 5.11-4.70 (m, 5H), 3.34 (m, 2H), 2.80 (m, 1H), 2.62 (m, 1H), 2.30 (m, 1H), 0.95 (m, 6H):MS [M+H] = 547

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.03 (d, 1H), 8.74 (d, 1H), 8.56 (d, 1H), 8.20-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.23 (m, 2H), 6.88 (m, 3H), 5.09-4.71 (m, 5H), 3.34 (m, 2H), 2.85 (m, 1H), 2.65 (m, 1H), 2.27 (m, 1H), 0.96-0.87 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo

xy)-pentanoic acid (compound 42)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.91 (d, J = 9.2 Hz, 1H), 8.59-8.52 (m, 2H), 8.17-8.06 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.58-7.53 (m, 5H), 4.69-4.51 (m, 4H), 3.40 (m, 2H), 3.16 (m, 1H), 2.69 (m, 1H), 2.37 (m, 1H), 2.19 (m, 1H), 0.91-0.80 (m, 6H): MS [M+H] = 733

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.92 (d, J = 9.2 Hz, 1H), 8.56(m, 2H), 8.19-8.07 (m, 3H), 7.87 (m, 1H), 7.73 (m, 1H), 7.60-7.54 (m, 3H), 7.22-7.07 (m, 5H), 5.01-4.93 (ABq, J = 16.5 Hz, 2H), 4.75-4.62 (m, 2H), 3.46 (d, J = 18.4 Hz, 1H), 3.23-3.07 (m, 3H), 2.62 (dd, J = 17.0, 6.9 Hz, 1H), 2.37 (dd, J = 17.0, 6.0 Hz, 1H), 2.21 (m, 1H), 0.86-0.83 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 43)

From more polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.91 (d, J = 9.2 Hz, 1H), 8.62 (d, J = 8.3 Hz, 1H), 8.52 (d, J = 8.7 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 8.07 (m, 2H), 7.86 (m, 1H), 7.72 (m, 1H), 7.26-7.09 (m, 7H), 6.86 (m, 1H), 6.69 (d, J = 8.3 Hz, 2H), 4.71-4.63 (m, 2H), 4.54-4.46 (ABq, J = 17.9 Hz, 2H), 3.42 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 13.8 Hz, 1H), 3.15 (d, J = 18.4 Hz, 1H), 3.09 (d, J = 14.3 Hz, 1H), 2.72 (dd, J = 17.0, 6.9 Hz, 1H), 2.36 (dd, J = 17.0, 6.0 Hz, 1H), 2.15 (m, 1H), 0.88 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H): MS [M+H] = 637

From less polar isomer: ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.88 (d, J = 9.6 Hz, 1H), 8.54 (m, 2H), 8.18-8.06 (m, 3H), 7.87 (m, 1H), 7.72 (m, 1H), 7.28-6.78 (m, 10H), 4.78-4.63 (m, 4H), 3.45 (d, J = 18.3 Hz, 1H), 3.26-3.06 (m, 3H), 2.66-2.62 (dd, J = 17.0, 6.9 Hz, 1H), 2.44-2.39 (dd, J

= 17.0, 5.5 Hz, 1H), 2.17 (m, 1H), 0.80 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-imidazolylmethyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 44, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.09-6.60 (m, 16H), 4.92-4.62 (m, 6H), 3.50 (m, 2H), 2.85-2.20 (m, 3H), 0.93 (m, 6H): MS [M+H] = 627

· (3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid (compound 45, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.77 (m.1H), 8.45 (m, 2H), 8.07-7.89 (m, 4H), 7.61 (m, 2H), 5.06 (m, 1H), 4.72 (m, 1H), 4.46 & 4.38 (two m, 1H), ~3.3 (m, isoxazoline CH_2), 2.62 (m, 1H), ~2.49 (m, 1H), 2.13 (m, 1H), 2.09 & 2.05 (two s, 3H), 1.01-0.84 (m, 6H).

· (3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 46, diastereomeric mixture)

^{1}H-NMR (500 MHz,DMSO-d_6) δ 8.56-8.52 (m, 1H), 8.15 (m, 1H), 7.27 (m, 2H), 6.97-6.82 (m, 3H), 4.96-4.83 (m, 2H), 4.77 (m, 1H), 4.58 (m, 1H), 3.58-2.22 (m, 10H), 2.0-1.74 (m, 2H), 1.47 & 1.45 (two s, 3H):MS [M+Na] = 558.

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (compound 47, diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.62-8.52 (m, 1H), 8.06 (m, 1H), 7.27 (m, 2H), 6.96-6.81 (m, 3H), 4.94-4.72 (m, 3H), 4.43-4.32 (m, 1H),

3.38-3.22 (m, 1H), 2.94-2.78 (m, 2H), 2.70-2.22 (m, 5H), 1.95-1.77 (m, 1H), 1.48 & 1.46 (two s, 3H), 0.86-0.70 (m, 6H): MS [M+Na] = 528.

· (3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidinyl)-pentanoic acid (compound 48, diastereomeric)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.75 (m, 1H), 8.47 and 8.29 (m, 1H), 8.03-7.23 (m, 12H), 4.65 (m, 2H), 3.11-2.99 (m, 2H), 2.26-2.18 (m, 4H), 1.97 (m, 1H), 1.64-0.79 (m, 12H):MS [M+H] = 627.

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 49LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.03 (d, J = 9.2 Hz, 1H), 8.74 (d, J = 8.3 Hz, 1H), 8.60-8.56 (m, 2H), 8.07-8.03 (m, 2H), 7.83 (m, 1H), 7.73 (m, 1H), 7.61-7.53 (m, 3H), 7.22-7.17 (m, 5H), 5.01-4.93 (ABq, J = 17.0 Hz, 2H), 4.74-4.63 (m, 2H), 3.41 (d, J = 17.9 Hz, 1H), 3.23 (d, J = 14.2 Hz, 1H), 3.13 (d, J = 17,9 Hz, 1H), 3.09 (d, J = 14.2 Hz, 1H), 2.60 (m, 1H), 2.36 (m, 1H), 2.10 (m, 1H), 0.91 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 50LP: stereoisomer of 49LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.04 (d, J = 9.2 Hz, 1H), 8.65-8.60 (m, 2H), 8.53 (d, J = 6.0 Hz, 1H), 8.05-8.00 (m, 2H), 7.82 (m, 1H), 7.72 (m, 1H), 7.60-7.53 (m, 3H), 7.30-7.17 (m, 5H), 4.75-4.53 (m, 4H), 3.5-3.3 (m, 2H, buried under solvent peaks), 3.13 (m, 2H), 2.68 (m, 1H), 2.41 (m, 1H), 2.04 (m, 1H), 0.95 (d, J = 6.4 Hz, 3H), 0.78 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid (Compound 51LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.40 (s, 1H), 8.99 (d, J = 9.2 Hz, 1H), 8.56 (m, 2H), 8.26 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.90-7.81 (m, 2H), 7.60-7.53 (m, 3H), 7.20-7.07 (m, 5H), 5.01-4.92 (ABq, J = 17.0 Hz, 2H), 4.73-4.66 (m, 2H), ~3.4 (m, 1H, buried under solvent peaks), 3.23-3.05 (m, 3H), 2.60 (m, 1H), 2.34 (m, 1H), 2.19 (m, 1H), 0.82 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid(Compound 52MP: stereoisomer of Compound 51)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 8.97 (d, J = 9.6 Hz, 1H), 8.58 (d, J = 8.7 Hz, 1H), 8.53 (s, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.88-7.81 (m, 2H), 7.58-7.53 (m, 3H), 7.27-7.18 (m, 5H), 4.72-4.49 (m, 4H), 3.6-3.3 (m, 2H, buried under solvent peaks), 3.19-3.08 (m, 2H), 2.67 (m, 1H), 2.34 (m, 1H), 2.18 (m, 1H), 0.87 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-4-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid (Compound 53 LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.02 (m, 2H), 8.63 (d, J = 8.7 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.83 (m, 1H), 7.69 (m, 1H), 7.61-7.53 (m, 3H), 7.44 (d, J = 4.2 Hz, 1H), 7.31-7.20 (m, 6H), 4.98 (m, 2H), 4.76-4.65 (m, 2H), 3.37 (d, J = 17.9 Hz, 1H), 3.29 (d, J = 14.2 Hz, 1H), 3.15-3.11 (m, 2H), 2.63 (m, 1H), 2.39 (m, 1H), 1.99

(m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-4-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 54 MP: stereoisomer of Compound 53 LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.05 (d, J = 8.7 Hz, 1H), 8.96 (d, J = 4.1 Hz, 1H), 8.64 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.82 (m, 1H), 7.69-7.48 (m, 5H), 7.31-7.20 (m, 5H), 4.80-4.55 (m, 4H), 3.6-3.3 (m, 2H, buried under solvent peaks), 3.14-3.09 (m, 2H), 2.72 (m, 1H), 2.41 (m, 1H), 1.95 (m, 1H), 0.96 (d, J = 6.9 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 55LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.83 (d, J = 9.2 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.61-7.33 (m, 6H), 7.20-7.04 (m, 5H), 5.00-4.92 (m, 2H), 4.73 (m, 1H), 4.56 (m, 1H), ~3.37 (m, 1H), 3.23-3.05 (m, 3H), 2.61 (m, 1H), 2.36 (m, 1H), 2.08 (m, 1H), 0.88-0.78 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 56: stereoisomer of Compound 55LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.83 (d, J = 9.2 Hz, 1H), 8.55 (d, J = 8.7 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.58-7.43 (m, 5H), 7.33-7.18 (m, 6H), 4.69-4.55 (m, 4H), 3.43-3.30 (m, 2H), 3.12-3.07 (m, 2H), 2.69 (m, 1H), 2.37 (m, 1H), 2.06 (m, 1H), 0.90 (d, J = 6.4 Hz, 3H), 0.74 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-difluorobenzoylo xy)-pentanoic acid (Compound 57LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.77 (d, J = 9.7 Hz, 1H), 8.64 (d, J = 8.3 Hz, 1H), 8.06-7.95 (m, 3H), 7.69-7.44 (m, 5H), 7.26 (m, 7H), 5.02-4.90 (ABq, J = 17.0 Hz, 2H), 4.71 (m, 2H), 3.30-3.10 (m, 4H), 2.65 (m, 1H), 2.39 (m, 1H), 1.99 (m, 1H), 0.94 (d, J = 6.0 Hz, 3H), 0.84 (d, J = 6.0 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dimethylbenzoylo xy)-pentanoic acid(Compound 61: diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.82-8.76 (m, 1H), 8.65 (m, 1H), 8.08-7.95 (m, 3H), 7.59-7.46 (m, 4H), 7.33-7.06 (m, 8H), 4.98-4.49 (m, 4H), 3.42-3.09 (m, 4H), 2.76-2.39 (m, 2H), 2.28 & 2.25 (two s, 6H), 1.98 (m, 1H), 0.99-0.76 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(quinoline-8-carbonylamino)-propyl]-5-phenylmet hyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 62: diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.19-11.08 (m, 1H), 9.04 (m, 1H), 8.65-8.50 (m, 3H), 8.22 (m, 1H), 7.80-7.51 (m, 5H), 7.30-7.06 (m, 5H), 5.00-4.47 (m, 4H), 3.46-3.02 (m, 4H), 2.73-2.34 (m, 2H), 2.11 (m, 1H), 1.00-0.80 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl -4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pe ntanoic acid(Compound 63LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.58 (s, 1H), 8.56 (d, J = 8.7 Hz, 1H), 8.49 (d, J = 8.7 Hz, 1H), 7.64-7.53 (m, 4H), 7.43 (d, J = 8.3 Hz, 1H), 7.24-7.03 (m, 8H), 5.00-4.92 (ABq, J = 17.0 Hz, 2H), 4.74-4.56 (m, 2H), ~3.5 (m, 1H, buried under solvent peaks), 3.23 (d, J = 13.8 Hz, 1H), 3.15-3.06 (m, 2H), 2.60 (m, 1H), 2.35 (m, 1H), 2.02 (m, 1H), 0.90 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 64MP: stereoisomer of Compound 63LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.56 (s, 1H), 8.54 (m, 2H), 7.60-7.02 (m, 13H) 4.71-4.51 (m, 4H), , 3.41-3.31 (m, 2H), 3.15-3.07 (m, 2H), 2.67 (m, 1H), 2.38 (m, 1H), 2.05 (m, 1H), 0.92 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 65LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.56 (d, J = 8.3 Hz, 1H), 8.08 (m, 2H), 7.91 (d, J = 9.2 Hz, 1H), 7.62-7.54 (m, 3H), 7.43 (d, J = 8.3 Hz, 1H), 7.22-7.00 (m, 7H), 4.95 (m, 2H), 4.72-4.61 (m, 2H), ~3.4 (m, 1H, buried under solvent peaks), 3.23 (d, J = 13.8 Hz, 1H), 3.13-3.06 (m, 2H), 2.61 (m, 2H), 2.34 (m, 1H), 1.99 (m, 1H), 0.91 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 66MP: stereoisomer of Compound 65LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.54 (d, J = 8.7 Hz,

1H), 8.11-8.06 (m, 2H), 7.91 (d, J = 9.2 Hz, 1H), 7.60-7.05 (m, 11H), 4.71-4.47 (m, 4H), 3.33 (m, 2H), 3.09 (m, 2H), 2.68 (m, 2H), 2.39 (m, 1H), 2.00 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 67LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.86 (d, J = 9.2 Hz, 1H), 8.73 (d, J = 8.3 Hz, 1H), 8.11-7.98 (m, 3H), 7.64-7.54 (m, 7H), 5.17-5.08 (ABq, J = 17.0 Hz, 2H), 4.81-4.70 (m, 2H), ~3.4 (m, 1H, buried under solvent peaks), 3.05 (d, J = 17.9 Hz, 1H), 2.87 (m, 1H), 2.65 (m, 1H), 2.02 (m, 1H), 1.55 (s, 3H), 1.00 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 68MP: stereoisomer of Compound 67LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.84 (d, J = 8.7 Hz, 1H), 8.69 (d, J = 8.3 Hz, 1H), 8.06-7.96 (m, 3H), 7.62-7.52 (m, 7H), 5.23-5.11 (ABq, J = 17.0 Hz, 2H), 4.82-4.67 (m, 2H), 3.6-3.4 (m, 1H, buried under solvent peaks), 3.00 (d, J = 17.9 Hz, 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.05 (m, 1H), 1.56 (s, 3H), 1.01-0.93 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 69LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.91 (d, J = 8.7 Hz, 1H), 8.70 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.62-7.54 (m, 4H), 7.48 (m, 1H), 7.34 (m, 1H), 5.16-5.07 (ABq, J = 17.0 Hz, 2H), 4.79 (m, 1H), 4.61 (m, 1H), 3.44 (d, J = 17.9 Hz, 1H), 3.02 (d,

J = 17.9 Hz, 1H), 2.87 (dd, J = 17.0, 6.0 Hz, 1H), 2.65 (dd, J = 17.0, 7.4 Hz, 1H), 2.11 (m, 1H), 1.50 (s, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 70MP: stereoisomer of Compound 69LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.86 (d, J = 8.7 Hz, 1H), 8.62 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.60-7.52 (m, 4H), 7.45 (m, 1H), 7.31 (m, 1H), 5.14-5.07 (ABq, J = 17.0 Hz, 2H), 4.71 (m, 1H), 4.62 (m, 1H), 3.44 (d, J = 17.9 Hz, 1H), 3.00 (d, J = 17.9 Hz, 1H), 2.79 (dd, J = 17.0, 6.4 Hz, 1H), 2.56 (dd, J = 17.0, 6.0 Hz, 1H), 2.16 (m, 1H), 1.53 (s, 3H), 0.95-0.91 (m, 6H).

· (3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 71LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.60 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.61-7.54 (m, 3H), 5.16-5.08 (ABq, J = 17.0 Hz, 2H), 4.78 (m, 1H), 4.62 (m, 1H), 3.31 (d, J = 17.9 Hz, 1H), 2.90 (d, J = 17.9 Hz, 1H), 2.85 (dd, J = 17.0, 6.0 Hz, 1H), 2.64 (dd, J = 17.0, 6.9 Hz, 1H), 2.44 (m, 2H), 2.33 (m, 2H), 2.24 (m, 2H), 1.90-1.76 (m, 2H), 1.46 (s, 3H).

· (3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 72MP: stereoisomer of Compound 71LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.55 (d, J = 8.3 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 7.62-7.55 (m, 3H), 5.21-5.09 (ABq, J = 17.0 Hz, 2H), 4.76

(m, 1H), 4.58 (m, 1H), 3.23 (d, J = 17.9 Hz, 1H), 2.95 (d, J = 17.9 Hz, 1H), 2.83 (dd, J = 17.0, 6.5 Hz, 1H), 2.62 (dd, J = 17.0, 6.4 Hz, 1H), 2.44 (m, 2H), 2.33 (m, 2H), 2.25 (m, 2H), 1.96 (m, 1H), 1.80 (m, 1H), 1.50 (s, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 73LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.66 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.62-7.57 (m, 3H), 5.14-5.05 (ABq, J = 17.0 Hz, 2H), 4.77 (m, 1H), 4.36 (m, 1H), 3.31 (d, J = 18.4 Hz, 1H), 2.92 (d, J = 18.4 Hz, 1H), 2.87-2.83 (m, 1H), 2.66-2.61 (m, 1H), 2.44 (m, 1H), 2.37 (m, 1H), 1.84 (m, 1H), 1.48 (s, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.77 (d, J = 6.4 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 74MP: stereoisomer of Compound 73LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.56 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.62-7.57 (m, 3H), 5.19-5.08 (ABq, J = 17.0 Hz, 2H), 4.75 (m, 1H), 4.40 (m, 1H), 3.30 (d, J = 17.9 Hz, 1H), 2.93 (d, J = 17.9 Hz, 1H), 2.82 (m, 1H), 2.60 (m, 1H), 2.44-2.31 (m, 4H), 1.92 (m, 1H), 1.51 (s, 3H), 0.86-0.84 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 75LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.60 (m, 3H), 5.17-5.04 (ABq, J = 17.0 Hz, 2H), 4.83 (m,

1H), 4.37 (m, 1H), 3.25 (d, J = 17.9 Hz, 1H), 2.95 (d, J = 17.9 Hz, 1H), 2.85 (dd, J = 17.0, 5.5 Hz, 1H), 2.65 (dd, J = 16.5, 7.4 Hz, 1H), 2.46-2.35 (m, 4H), 1.84 (m, 2H), 1.70 (m, 1H), 1.36-1.15 (m, 2H), 0.88-0.76 (m, 9H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 76MP: stereoisomer of Compound 75LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.59 (d, J = 6.4 Hz, 1H), 8.07 (d, J = 9.2 Hz, 1H), 7.62-7.54 (m, 3H), 5.12 (m, 2H), 4.74 (m, 1H), 4.40 (m, 1H), 3.24 (d, J = 17.9 Hz, 1H), 2.95 (d, J = 17.9 Hz, 1H), 2.82 (dd, J = 17.0, 6.9 Hz, 1H), 2.59 (m, 1H), 2.44-2.30 (m, 4H), 1.92 (m, 2H), 1.71 (m, 1H), 1.38-1.20 (m, 2H), 0.85 (m, 9H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 79LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.63 (d, J = 8.2 Hz, 1H), 8.09 (d, J = 9.2 Hz, 1H), 7.62-7.57 (m, 3H), 5.17-5.05 (ABq, J = 17.0 Hz, 2H), 4.83 (m, 1H), 4.37 (m, 1H), 3.25 (d, J = 17.9 Hz, 1H), 2.95 (d, J = 17.9 Hz, 1H), 2.85 (dd, J = 17.0, 5.5 Hz, 1H), 2.65 (dd, J = 17.0, 7.3 Hz, 1H), 2.45-2.35 (m, 4H), 1.84 (m, 2H), 1.71 (m, 1H), 1.28-1.14 (m, 4H), 0.88-0.76 (m, 9H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 80MP: stereomeric isomer of Compound 79LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.58 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.61-7.54 (m, 3H), 5.18-5.08 (ABq, J = 17.0 Hz, 2H), 4.76

(m, 1H), 4.40 (m, 1H), 3.24 (d, J = 17.9 Hz, 1H), 2.95 (d, J = 18.3 Hz, 1H), 2.83 (dd, J = 16.5, 6.4 Hz, 1H), 2.59 (dd, J = 17.0, 6.4 Hz, 1H), 2.44-2.30 (m, 4H), 1.92 (m, 2H), 1.73 (m, 1H), 1.36-1.16 (m, 4H), 0.87-0.83 (m, 9H).

· (3S)-3-{3-[2-methyl-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid (Compound 81LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.67 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.83 (m, 2H), 7.73 (d, J = 7.8 Hz, 1H), 7.46 (m, 1H), 7.36 (m, 1H), 7.18 (m, 2H), 5.01 (m, 2H), 4.83 (m, 1H), 4.34 (m, 1H), 3.30 (d, J = 17.4 Hz, 1H), 2.93-2.87 (m, 2H), 2.67 (dd, J = 17.0, 6.4 Hz, 1H), 2.45-2.34 (m, 4H), 1.79 (m, 1H), 1.49 (s, 3H), 0.80 (d, J = 6.5 Hz, 3H), 0.68 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid (Compound 82MP: stereomeric isomer of Compound 81LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.58 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.83 (m, 2H), 7.73 (d, J = 7.8 Hz, 1H), 7.46 (m, 1H), 7.35 (m, 1H), 7.18 (m, 2H), 5.04 (m, 2H), 4.82 (m, 1H), 4.40 (m, 1H), 3.33 (d, J = 17.4 Hz, 1H), 2.95-2.82 (m, 2H), 2.65 (m, 1H), 2.44-2.27 (m, 4H), 1.91(m, 1H), 1.51 (s, 3H), 0.86-0.83 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid(Compound 83: diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.57 (m, 1H), 8.06 (m, 1H), 7.26 (m, 2H), 6.94 (m, 1H), 6.83 (m, 2H), 4.92-4.71 (m, 3H), 4.41-4.34 (m, 1H),

3.26-3.21 (m, 1H), 2.96-2.78 (m, 2H), 2.67-2.56 (m, 1H), 2.44-2.25 (m, 4H), 1.92-1.66 (m, 3H), 1.40-1.16 (m, 2H), 0.88-0.70 (m, 9H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-hydroxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 84: diastereomeric mixture)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.57 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.7 Hz, 1H), 7.59 (m, 3H), 5.24-5.09 (m, 2H), 4.80 (m, 1H), 4.40 (m, 1H), 3.78 (m, 1H), 3.56 (m, 1H), 3.16-3.03 (m, 2H), 2.79 (m, 1H), 2.60 (m, 1H), 2.44-2.33 (m, 4H), 1.90 (m, 1H), 0.86-0.76 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 85LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.51 (d, J = 8.8 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.59 (m, 3H), 7.25 (m, 5H), 4.92 (ABq, J = 17.0 Hz, 2H), 4.70 (m, 1H), 4.34 (m, 1H), 3.34-3.20 (m, 2H), 3.07-3.02 (m, 2H), 2.58 (m, 1H), 2.44-2.30 (m, 5H), 1.82 (m, 1H), 0.81-0.73 (m, 6H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 86MP: diastereomer of Compound 85LP)
^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.49 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.60 (m, 3H), 7.28-7.19 (m, 5H), 4.70 (m, 1H), 4.60-4.51 (ABq, J = 17.4 Hz, 2H), 4.36 (m, 1H), 3.32-3.26 (m, 2H), 3.07-3.02 (m, 2H), 2.73-2.68 (m, 1H), 2.42-2.28 (m, 5H), 1.82 (m, 1H), 0.83 (d, J = 6.9 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methoxymethyl-4,5-

dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 87: diastereomeric mixture)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.80 & 8.65 (two m, 1H), 8.10 & 7.97 (two m, 1H), 7.60 (m, 3H), 5.24-5.03 (m, 2H), 4.84 & 4.68 (two m, 1H), 4.39 (m, 1H), 3.78-3.51 (m, 2H), ~3.35 (two s, 3H), 3.20-2.99 (m, 2H), 2.91-2.50 (m, 2H), 2.44-2.34 (m, 4H), 1.85 (m, 1H), 0.87 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 89LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 8.3 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.60 (m, 3H), 5.16-5.05 (ABq, J = 16.5 Hz, 2H), 4.80 (m, 1H), 4.36 (m, 1H), 3.24 (d, J = 17.5 Hz, 1H), 2.94 (d, J = 17.9 Hz, 1H), 2.85 (m, 1H), 2.64 (m, 1H), 2.45-2.36 (m, 4H), 1.84 (m, 2H), 1.70 (m, 1H), 1.23 (m, 6H), 0.86-0.76 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 90MP: diastereomer of Compound 89LP

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.59 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.60 (m, 3H), 5.18-5.08 (ABq, J = 16.5 Hz, 2H), 4.76 (m, 1H), 4.40 (m, 1H), 3.24 (d, J = 18.3 Hz, 1H), 2.95 (d, J = 18.3 Hz, 1H), 2.82 (m, 1H), 2.58 (m, 1H), 2.44-2.30 (m, 4H), 1.92 (m, 2H), 1.72 (m, 1H), 1.23 (m, 6H), 0.85 (m, 6H).

. (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 91LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.66 (d, J = 8.3 Hz, 1H), 8.10 (d, J =

8.7 Hz, 1H), 7.62-7.56 (m, 3H), 5.17-5.05 (ABq, J = 16.5 Hz, 2H), 4.84 (m, 1H), 4.36 (m, 1H), 3.25 (d, J = 17.9 Hz, 1H), 2.95 (d, J = 17.9 Hz, 1H), 2.85 (m, 1H), 2.65 (m, 1H), 2.45-2.35 (m, 4H), 1.91-1.71 (m, 3H), 0.88-0.74 (m, 9H).

· (3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 92MP: diastereomer of Compound 91LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.59 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.62-7.54 (m, 3H), 5.17-5.09 (ABq, J = 17.0 Hz, 2H), 4.75 (m, 1H), 4.40 (m, 1H), 3.23 (d, J = 18.3 Hz, 1H), 2.95 (d, J = 17.8 Hz, 1H), 2.83 (m, 1H), 2.61 (m, 1H), 2.46-2.28 (m, 4H), 1.93 (m, 2H), 1.77 (m, 1H), 0.88-0.80 (m, 9H).

· (3S)-3-{3-[2-methyl-(1S)-1-(glutaroylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid (Compound 93LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.66 (d, J = 8.7 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.61-7.54 (m, 3H), 5.14-5.05 (ABq, J = 16.5 Hz, 2H), 4.79 (m, 1H), 4.40 (m, 1H), 3.32 (d, J = 17.5 Hz, 1H), 2.90-2.83 (m, 2H), 2.63 (m, 1H), 2.18 (m, 4H), 1.85 (m, 1H), 1.72 (m, 2H), 1.48 (s, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H).

· (3S)-3-{3-[2-methyl-(1S)-1-(glutaroylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid(Compound 94MP: diastereomer of Compound 93LP)

^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.58 (d, J = 7.8 Hz, 1H), 8.05 (d, J = 9.2 Hz, 1H), 7.62-7.54 (m, 3H), 5.18-5.08 (ABq, J = 17.0 Hz, 2H), 4.76 (m, 1H), 4.41 (m, 1H), 3.31 (d, J = 17.4 Hz, 1H), 2.92 (d, J = 17.9 Hz,

1H), 2.80 (m, 1H), 2.60 (m, 1H), 2.16 (m, 4H), 1.91 (m, 1H), 1.70 (m, 2H), 1.51 (s, 3H), 0.85 (m, 6H).

Pharmacological Experiments

The pharmacological efficacy of the compound according to the present invention was evaluated by the following experiments. Con A was purchased from Boehringer Mannheim GmbH (Mannheim, Germany). Peptide-based substrates of caspases (Ac-YVAD-pNA for caspase-1, Ac-VDVAD for caspase-2, Ac-DEVD-pNA for caspase-3, 7, 8, and 9, Ac-LEVD-pNA for caspase-4, and Ac-VEID-pNA for caspase-6) and peptide-based caspase inhibitors (Ac-DEVD-fmk, z-VAD-CHO) were purchased from Alexis Co. (San Diego, CA). Ac-DEVD-CHO and z-DEVD-cmk were purchased from Bachem; Anti Fas antibody was purchased from Oncor (Cat#A8050); WI38 cell was available from ATCC; IFN-gamma was purchased from LG Pharmaceuticals (Korea). All cell culture-media and supplements were purchased from Gibco BRL (Tsuen Wan, Hong Kong) unless mentioned otherwise. Recombinant human caspases(1-4, 6-10) were prepared according to the method described in Garcia-Calvo M et al., "Purification and catalytic properties of human caspase family members", *Cell Death Differ.*, 1999, Apr.; 6(4): 362-9). Especially Caspase-3, -6, -7 and -8 are commercially available (Pharmingen, SanDiego, CA, USA, Caspase-3: 66281T, Caspase-6: 66291T, Caspase-7: 66301T, Caspase-8: 66311T).

Experiment 1: Screening on caspases inhibiting activity

In the present experiment, recombinant caspases were purified from a transformed bacterium after human caspase genes were cloned into the

expression vector pET, and then used in the experiment (Thornberry, N.A. et .al. *Nature*, 1992, *356*, 768. Thornberry, N.A. *Methods in Enzymology*, 1994, *615*.).

Enzymatic activity was measured by a known procedure (Walker N.P.C. et al., *Cell* 1994, *78*, 343). Briefly, 10 ng of recombinant protein was mixed with 50 mM Tris(pH 7.0), 1mM DTT, 0.5 mM EDTA, 10% Glycerol buffer containing 1~100 μM of enzyme substrate, Ac-YVAD-AMC or Ac-DEVD-AMC and then the changes by isolated AMC at 37°C were recorded. The inhibitory activity for caspases was calculated from the early enzyme reaction rate by measuring the changes with fluorescence excited at 380 nM and emitted at 460 nm (Range; Ki<100nM).

Experiment 2: Screening for intracellular inhibitory efficacy for caspases

Inhibitory activity for Caspase-1 was determined by screening the effects of the compounds on the IL-1β production in the periphery lymphocytes stimulated with LPS. Briefly, 500,000 cells/ml of human peripheral lymphocytes were treated with the test compounds at various concentrations for 2 hours and then with 10 ng/ml of LPS. After incubating the cells for 12 hours, the supernatant samples from the media were analysed by immunoantibody analysis (Amersham) in which 100 ng/well of human IL-1 β antibody is coated (Range: CIC_{50} : 0.1 ~ 10 μM).

Meanwhile, the efficacy of the compounds on apoptosis was quantified by MTT assay in which cell death and survival ratio depending on the concentration of compounds were analyzed in Jurkat T cell treated with Anti-FAS antibody CH11 which induces cell death (Effective range; 1.0 ~ 10 μM).

[Table 1]

Irreversible Inhibitors

compound no.	Kobs/[I] for caspase-1 ($M^{-1}sec^{-1}$)	Kobs/[I] for caspase-3 ($M^{-1}sec^{-1}$)	CIC_{50} (IL-1 β production)	ED_{50} FAS Induced cell death
32	130000	114	0.1-10 μM	1-10 μM
33mp	807000	500	"	"
36mp	294000	132	"	"
42mp	408000	160	"	"
58	577000	371	"	"
64	707000	1230	"	"
66	357000	1560	"	"
68	616000	2390	"	"
72	30800	176000	"	"
74	14500	40900		
76	14000	197000	"	"
80	14900	1140000	"	"
86	7560	28000		
87	3400	27400		
90		80100		

Reversible Inhibitor

compound no.	Ki for caspase-1 (nM)	Kobs/[I] for caspase-3 (uM)	CIC_{50} (IL-1 β production)	ED_{50} FAS Induced cell death
22mp	0.125	19.2	0.1-10 μM	1-10 μM
25mp	0.0721	24.9	"	"
29	0.324	65.9	"	"
30	19.1	44.8	"	"
43mp	4.0	70.7	"	"
46	29.1	0.0806	"	"
47	177	0.85	"	"
48	1.51	199	"	"
77	28900	19.3	"	"
78	63900	45.5		
81	26900	11.7	"	"
82	530	0.184	"	"
83	969	0.0277		

Experiment 3: Hepatocyte isolation and cultivation

Male Sprague-Dawley rats (Hanlan Sprague-Dawley) were treated and bred as described by MacMicking et al., 1995, *Cell* 81: 641-650), and used as a source of liver cells. Rat hepatocytes were isolated, purified, and cultured as described by Stadler et al., *Arch. Biochem. Biophys.* 302: 4-11). Highly purified hepatocytes (>98% purity and >98% viability by trypan blue exclusion) were suspended in Williams medium E containing 10% calf serum supplemented with 15 mM HEPES (pH 7.4), 1_{μ} M insulin, 2 mM L-glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin. The cells were plated on collagen-coated plates with a density of 2x 10^5 cells/well in a 12-well plate for cell viability test or 5x10^6 cells/ 100 ml dish for enzyme assay.

Experiment 4: In vitro assay for inhibition of caspase activity in cell free

system

Caspase activity was tested by measuring proteolytic cleavage of peptide-based chromogenic substrate by each enzyme. Recombinant human caspase was preincubated with 5 mM DTT in assay buffer (100 mM HEPES, pH 7.4, containing 20% (v/v) glycerol) for 20 minutes at room temperature. Aliquots of the enzyme (2 $\mu\ell$ containing catalytic activity of 0.2 absorbance at 405 nm/h) were mixed with 150 $\mu\ell$ of 200 μ M chromogenic substrate in the presence or absence of 100 μ M compound 33 in 96-well plates. The mixture was incubated at 37℃. The absorbance of enzymatically released pNA was measured discontinuously at 405 nm in a microplate reader for 1 hr. The caspase activity was calculated from initial velocity (mean± SE)(n=4, in which n represents the number of repeated experiment). As a result, the compound of the invention almost completely inhibited all tested caspase activity, only except for caspase 2 (Figure 1). This result indicates that the compound of the invention is a broad-spectrum caspase inhibitor.

Experiment 5: In vivo assay for inhibition of caspase activity in rat hepatocytes

Freshly isolated rat hepatocytes were treated with 2,000 units/ml TNF_α plus 100 ng/ml actinomycin D to induce cellular apoptosis. The cells were harvested after 10 hrs. Cytosolic solution was obtained by lysing cells with three cycles of freezing and thawing and centrifuging at 12,000 x g for 20 min. at 4 ℃. Cytosol (~2 μg of protein) was mixed with 200 μ M specific chromogenic substrate in 100 mM HEPES buffer (pH 7.4) containing 20% glycerol and 5 mM DTT in presence or absence of 100 μ M compound 33 and incubated 37 ℃. The caspase activity was

assayed by measuring the increased absorbance at 405 nm.

Strong enzyme activities were detected with Ac-DEVD-pNA (caspase-3, 7, 8 and 9), Ac-LEVD pNA (caspase-4), and Ac-VEm-pNA (caspase-6), and moderate enzyme activity was detected with Ac-VDVAD (caspase-2) (Figure 2). The compound of the invention almost completely inhibited these amplified caspase activities, and the activity was comparable with peptide-based caspase inhibitors Ac-DEVD-fmk and z-VAD-CHO (Figure 2). For Ac-YVAD-pNA (caspase-1), detected enzyme activity was relatively weak. However, the compound of the invention inhibited 74.1% of caspase-1-like activity.

Experiment 6: In vitro assay for enhancement of cell viability in isolated rat hepatocytes

The cells were treated with 2,000 units/ml TNF_{α} plus 100 ng/ml actinomycin D with or without 100 μ M caspase inhibitor(compound 33) for 12 hrs. Then cell viability was measured by crystal violet staining method (n=4).

As a result, the compound of the invention prevented the death of rat hepatocytes (mean$\pm$ SE)(Figure3). The result of this experiment indicates that the compound of the invention protected hepatocytes from apoptotic death induced by TNF_{α} plus actinomycin D.

Experiment 7: Effect on Con A-induced acute hapatitis mice

Step 1: Preparation of blood sample

Female 6-week-old Balb/c mice (Charles River Laboratory, Osaka, Japan) were kept at 22 ℃ and 55% relative humidity in a 12-h day/night rhythm with free access to food and water. Con A was dissolved in pyrogen-free saline to a concentration of 2.5 mg/ml and was injected via the tail vein in an amount of 20㎎/㎏ based on Con A. The animals were i.p. injected twice with compound 33 dissolved into a vehicle which consists of olive oil and 10% DMSO, or a vehicle alone, at 1 hr before and 4h after Con A injection. Animals were sacrificed by cervical dislocation at 24 hrs after Con A injection to obtain liver and blood samples.

Step 2: Assay for plasma aminotransferase activity

Blood samples obtained at step 1 were collected at 24h after Con A injection. Plasma AST and ALT activity were measured using Autokit (Youngdong Pharmaceutical Co., Seoul, Korea) following manufacturer's instruction.

Two independent experiments were performed to confirm the result. In the two experiments, ConA induced dramatic elevation of serum AST and ALT activity, and compound 33 suppressed the elevated enzyme activities in a dose-dependent manner (Figure 4A, B). In the second experiment (Figure 4B), the differences between Con A/vehicle group and Con A/4mg/kg compound 33 group did not reached at statistically significant level (AST : p=0.2972, ALT : p=0.1378) since enzyme activities of each mouse showed some variation. However, in 20 mg/kg of compound 33 group, AST and ALT activities were definitely reduced compared with ConA/vehicle group (AST: p=0.0174, ALT: p=0.0011). In the first experiment (Figure 4A), compound 33 slightly increased AST activity by itself but this increase did not reach at statistically significant level

(p=0.1033). These results indicate that the compound of formula (I) suppressed the elevated AST and ALT activities induced by Con A in vivo, but did not provoke significant liver toxicity by itself.

Step 3: Cytokine assay

Although a large part of the pathogenesis of hepatic disease remains vague, several lines of evidence suggest that cytokines may be involved in the hepatic injury directly or by activating the immune system, and cytokine including TNF_{α} , IL-2, IL-4, and IFN_{γ} by sandwich ELISA were reported to increase in patients with liver disease (See: Chisari, F. V., 1992, *Mol. Genet. Med.* 2: 67-104; Fukuda, R. et al., *Clin. Exp. Immunolol.* 100: 446-451; Yoshioka, K. et al., *Hepatology* 10: 769-773). Therefore, the present inventors assessed the effect of the present compound to serum cytokine concentrations elevated by Con A.

Blood samples were collected at 6 hrs after Con A injection at step 1. Murine IL-1β (Endogen Inc. Bostone, MA), IL-2, IL-4, IFN_{γ} (Pharmingen, San Diego, CA) amounts in plasma were measured by ELISA kits. The assays were performed exactly as described by the manufacturer. Each sample was determined twice.

The results showed that the compound of the invention suppressed the Con A-induced elevation of IL-1β in a dose-dependent manner (see Figure 5). Meantime, the compound of the invention moderately reduced IL-4 concentration showing a dose-dependent tendency, but the differences between treat groups did not reach at statistically significant level. On the other hand, the compound of the invention did not significantly affect IL-2 and IFN_{γ} concentrations. The compound of the invention itself slightly

reduced all four cytokines compared with vehicle alone, but those differences did not reach at statistically significant level ($0.05<p<0.95$ for all 4 cytokines).

Experiment 8: Histologic examination and detection of apoptosis

The present inventors estimated the prevalence of apoptotic cells in the mouse liver to certify the apoptosis-blocking effect of the compound of the present invention specifically in hepatocytes. Mice were treated ConA in the presence or absence of various dosages of compound 33 [A and G: ConA and vehicle treatment, B and H: ConA and compound 33 4㎎/㎏ treatment, C and I: ConA and compound 33 20㎎/㎏ treatment, D and J: ConA and compound 33 100㎎/㎏ treatment] to prepare frozen liver sections. Also, mice were treated with PBS and vehicle (E and K), or PBS and compound 33 100㎎/㎏ (F and L) to prepare frozen liver sections. Freshly excised mouse liver was immediately immersed in 25 % sucrose solution at 4 ℃ for overnight, then frozen in liquid nitrogen, and cryosectioned into 4 ㎛.

For histological examination, liver sections were fixed in 1% buffered paraformaldehyde and stained with hematoxilin & eosin (Fig. 6A to F). To detect apoptotic cells in liver, frozen liver was stained using an ApopTag *in situ* apoptosis peroxidase detection kit (terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling: TUNEL assay) (Oncor, Gaithersburg, MD) and DAKO liquid DAB (DAKO, Carpinteria, CA)(Fig. 6G to L). Staining was conducted according to manufacturer's instruction. After completion of staining, the samples were observed under an optical microscope. Each photograph represents typical results obtained from 10 mice per group. Histological examinations

revealed that Con A induced severe morphological and histological changes to hepatocytes (Figure 6 A) and the apoptotic lesions were clearly detectable through the affected liver (Figure 6 G). However, in the liver of mice treated with the compound of the invention(Compound 33), the apoptotic lesions were reduced dose-dependently (Figure 6B-D), and cellular histology were gradually recovered with increasing dose of compound 33 (Figure 6 H-J). These results indicated that the compound of the invention protected hepatocytes from the fatal apoptogenic effect of ConA.

Experiment 9: Western blotting

In this experiment, the cleavage of PARP was identified by the appearance on Western blot analysis of an 85 kDa-cleavage product in hepatic cell lysate obtained from mice treated with Con A and various doses of the compound of formula (I).

Freshly harvested livers treated with Con A or PBS together with various doses of compound 33 were rinsed in cold PBS and homogenized into three volumes per weight of cold PBS containing 1% Nonidet P-40, 0.1 % SDS, 1 mM PMSF, and protease inhibitor cocktail tablet Complete™ (Boehnger Mannheim, used according to manufacturer's instruction). The homogenates were incubated on ice for 30 min. Samples were then centrifuged at 16,000 x g for 30 min at 4℃. Supernatants were transferred to fresh tubes and centrifuged for additional 30 min. Harvested lysates were precleared by incubating with protein G-sepharose (Pharmacia, Uppsala, Sweden) at 4 ℃ for overnight, gently shaking. Supernatants were harvested by centrifugation at 1000 x g for 30 sec. at 4 ℃ and separated on 7 % SDS-polyacrylamide gel and transferred to nitrocellulose

membrane. Blots were blocked for 1 hr at room temperature in PBS containing 5% skimmed milk and 0.1% Tween 20 under gentle shaking. Membranes were then incubated overnight with 1:1000 diluted monoclonal anti-PARP antibody (Pharmingen) under gentle shaking. After washing three times with PBS-Tween, the blots were hybridized with goat anti-mouse IgG-horse radish peroxidase (1:1000 dilution). After washing three times PBS-tween, signals were developed with ECL Western blotting kit (Amersham-Pharmacia Biotech, San Francisco, CA) and visualized by autoradiography.

In accordance with histological examination, the compound of the invention inhibited PARP cleavage caused by Con A-induced apoptotic death of hepatic cells (Figure 7). The apoptosis-blocking effect of the compound appeared in a dose-dependent manner.

Experiment 10: Effect of the caspase inhibitor on the protection of apoptosis

In order to determine the efficacy of the compound according to the present invention on the protection of apoptosis, the following experiments were conducted.

WI38 cells (human embryonal lung fibroblast) were grown in a medium containing DMEM-10% FBS within 10_{cm} diameter dishes until reaching at confluency. The cells were seeded into a 24-well plate at day 1 and incubated overnight while the volume of medium was maintained to $400\mu\ell$. Cells were treated with 200 units/$m\ell$ of IFN_γ at day 2 and incubated over 12 hrs or more. At day 3, each 100 $\mu\ell$ of test compound was added to the cells after diluting the 10mM stock compound in DMSO to final

concentrations of 50, 10, 2, and 0.4 μ M, respectively. The cells were incubated for 2 hrs in order for allowing the compound to enter into the cells and then treated with 40ng/well of anti-Fas antibody(apoptosis was induced 2 hrs after antibody was treated and the incubation was continued overnight). The control was not treated with Fas antibody. At day 4, after cells were observed with a microscope, 300㎕ of medium per well and then 150㎕ of XTT working solution were added to the medium and cultivation was continued for 2 hrs. After coloring, 100-200㎕ of the supernatant was transferred to a 96-well plate and the absorbance at 490 nm was read with ELISA plate reader. For the blank, XTT solution was added to the well containing the medium only. Plotting was determined by comparing with the control group (100% when Fas antibody was not treated). The results thereof are shown in Table 2 below.

[Table 2]

Conc.(μ M)	IFN	IFN+Fas Ab	Ac-DEVD-CHO	z-DEVD-cmk	Comp 22	Comp 28	Comp 33
0	100	15.37					
0.4			12.16	15.13	14.44	14.67	15.51
2			14.75	16.27	18.32	17.33	64.44
10			19.16	27.38	35.37	82.40	92.68
50			35.14	47.32	78.29	90.39	100.21

As can be seen from the above table 2, only 15% of cells were survived when treated with the both IFN_{γ} and the anti-Fas antibody together while the existing caspase inhibitors, Ac-DEVD-CHO(reversible inhibitor) or z-DEVD-cmk(irreversible inhibitor) treatment (50μ M) resulted in viability

ratio of 35.1% and 47.3%, respectively. However, when treated with compound 22, compound 28, and compound 33 according to the invention at the same concentration, viability ratio was increased to 78%, 90%, 100%, respectively. Therefore, it is noted that the caspase inhibitors according to the invention prevented apoptosis much stronger than the existing drugs (See Fig. 8).

Experiment 11: Effect of the caspase inhibitor on anti-Fas antibody-induced liver apoptosis

Step A: Animal treatment

3-4 Weeks-old C57BL/6 female mice(18-20 g) were injected i.p. with compound 33MP dissolved in vehicle which consists of olive oil and 10% DMSO, or vehicle alone, at 1 hr before i.v. injection with 10 μg of Anti-Fas antibody (Jo2). Following 4 hrs of i.v. injection with Jo2 antibody, animals were placed under inhaled isoflurane anesthesia for blood collection and liver isolation. Mice were also i.p. injected with 0.2 μg/20 g of TNF_α and 12 mg/20 g of D-galactosamine(TNF_α /GalN) and compound 33MP or its salt form (Compound 33MP-Na). 8 hrs later, blood and liver tissues were isolated from anesthetized animals. The liver tissues were snap-frozen and stored at -80° C until use. Plasma was isolated from blood by centrifugation at 12,000 x g for 10 min at 4° C and stored at -80° C. In some experiments for animal mortality, mice were i.p. injected with TNF_α /GalN and caspase inhibitor was injected 1 hr before, simultaneously, 2 hrs, or 4 hrs after TNF_α /GalN injection.

Step B: DNA fragmentation

Whole tissues (0.5 g) were homogenated in ice-cold lysis buffer (5 mM Tris, 20 mM EDTA, 0.5% Triton-X 100, pH8.0). The lysate was centrifuged at 12,000 x g for 20 min at 4° C. The supernatant was obtained and extracted twice with a mixture of phenol and chloroform. One-tenth volume of 3 M sodium acetate was added to the solution, and DNA was precipitated by adding an equal volume of isopropanol. After storing at -20° C overnight, a DNA pellet was obtained by centrifugation at 12,000 x g for 15 min. at 4 ° C and washed twice with 75% ethanol. The pellet was dried and resuspended in 100 μl of 20 mM Tris-HCl, pH 8.0. After digesting RNA with DNase-free RNase (0.1 mg/ml) at 37 ° C for 1 hr, samples (15 ml) were electrophoresed through a 1.2% agarose gel in 450 mM Tris borate + EDTA (TBE), pH 8.0 buffer. DNA was photographed under visualized with UV light.

Step c: Enzyme assay

Liver tissues were homogenated in 10 mM HEPES buffer containing protease inhibitors (5 μg/ml aprotinin, 5 μg/ml pepstatin A, 10 μg/ml leupeptin, and 0.5 mM PMSF) and lysed by three freeze/thaw cycles. The cytosolic fraction was obtained by centrifugation at 12,000 x g for 20 min. at 4° C. Protein concentration was determined with BCA protein assay reagent (pierce, Rockford, IL). Cytosol containing 200 μg protein was combined in 96-well plate with 200 mM of synthetic substrate Ac-DEVD-pNA in 150 μl of 100 mM HEPES, pH 7.4, containing the protease inhibitors, and the reaction was conducted for 1 hr at 37° C. Cytosolic caspase-3-like activity was assayed by measuring the increased absorbance at 405 nm. Plasma level of aspartate aminotransferase (AST) was analyzed by spectrophotometry using each enzyme assay kit (Sigma).

Step D: Hepatocyte culture and treatment

Primary rat hepatocytes were isolated and purified from male Sprague-Dawley rats using a collagenase digestion method. The hepatocytes were purified over 30% Percoll gradient by centrifugation at 1,000 x g for 10 min. at 4° C. Highly purified hepatocytes (>98% purity and >95% viability by trypan blue exclusion) were suspended in Williams medium E supplemented with 10% calf serum, 1 μM insulin, 2 mM L-glutamine, 15 mM HEPES (pH 7.4), 100 units/ml penicillin, and 100 μg/ml streptomycin. The cells were plated on collagen-coated tissue culture plates at a density of 2 x 10^5 cells/well in 12-well plates for cell viability analysis or 5 x 10^6 cells/100 mm dish for enzyme assays. After 18 hrs preculture, the cells were treated with 2,000 units/ml TNF_α and 0.2 μg/ml Actinomycin (ActD). Caspase activity and cell viability was determined by colorimetry using a caspase substrate Ac-DEVD-pNA and crystal violet staining method at 8 hrs and 12 hrs, respectively.

As can be seen from the result of Fig. 9A, liver apoptosis from the mice injected with 0.4 mg/20 g, 1 mg/20 g of compound 33MP, or vehicle alone (olive oil and 10% DMSO) 1 hr before the antibody injection, as determined by DNA fragmentation, was significantly increased in anti-Fas antibody-injected animals after 4 hrs of the antibody injection. Treatment with compound 33MP was suppressed the liver apoptosis in a dose-dependent manner. The suppression was higher than that of well-known peptide caspase inhibitor Z-VAD-fmk. Similarly, the release of liver enzyme, AST was increased in animal treated with anti-Fas antibody (Fig. 9B). The enzyme release was also significantly suppressed by the injection with compound 33MP. This suppressive effect was higher than that of Z-VAD-fmk. These results indicate that compound 33MP can

protect liver from anti-Fas antibody-induced liver damage. As the activation of caspase-3-like proteases is required for execution phase of apoptosis, caspase-3-like activity was assessed after anti-Fas antibody injection by measuring hydrolytic product of the caspase-3-like substrate Ac-DEVD-pNA at 405 nm. Caspase activity was increased by about 25-folds in liver tissues treated with the antibody (Fig. 10). The increased activity was abrogated by compound 33MP treatment. Furthermore, most of anti-Fas antibody-treated animals (85%) died within 24 hrs, whereas treatment with compound 33MP reduced mortality by about 30% (Fig. 11). This inhibition was more effective than that of Z-VAD-fmk. This result suggests that inhibition of caspase activity and/or activation by compound 33MP is sufficient to protect mice from anti-Fas antibody-induced apoptotic mortality.

Liver dysfunction and failure are common problems during endotoxemia and sepsis. It is generally accepted that proinflammatory cytokines, especially TNF_{α} , are critical for the liver damage and mortality. We examined the effect of compound 33MP on TNF_{α} -mediated liver toxicity. Treatment with TNF_{α} /ActD induced DNA fragmentation in liver tissues and this toxicity was significantly reduced by administration of compound 33MP (Fig. 12A). The release of AST following TNF_{α} /ActD treatment was also suppressed by treatment with compound 33MP (Fig. 12B). The protective effect of compound 33MP was higher than that of Z-VAD-fmk. TNF_{α} /ActD-mediated liver toxicity was accompanied by increase in caspase-3-like activity (Fig. 13). The increased caspase activity was suppressed by compound 33MP, which showed higher inhibitory effect than Z-VAD-fmk. These data indicate that the suppression of proapoptotic caspase activity by compound 33MP is correlated with the suppression of liver damage with apoptotic DNA fragmentation. Since fulminant liver

damage and destruction are associated with animal mortality, we examined the effect of the compound of the invention on TNF_α /ActD-mediated mouse mortality. When injected with TNF_α /ActD and vehicle (olive oil and 10% DMSO), most of mice (~80%, 1 of 6) died within 24 hrs, whereas 80% of compound 33 MP-treated animals survived (Fig. 14). Similar results were obtained by injection with Z-VAD-fmk. Thus, our results suggest that new non-peptide caspase inhibitor according to the invention may have therapeutic applications in the treatment of fulminant liver damage.

The inventors prepared the sodium salt form of compound 33 MP to increase its solubility and examined the effect of this compound (Compound 33MP-Na) on caspase activity and cell viability in TNF_α /ActD-treated primary rat hepatocytes. Caspase-3-like activity was increased in cultured hepatocytes following treatment with TNF_α /ActD for 8 hrs (Fig. 15A). This increase was suppressed by adding 100 μM compound 33MP-Na and this inhibition was not different from those of compound 33MP, Ac-DEVD-cho, or Z-VAD-fmk. Treatment with TNF_α /ActD decreased cultured hepatocyte viability to about 30%, whereas all caspase inhibitors showed the similar protective effects on TNF_α /ActD-induced hepatocyte apoptosis (Fig. 15B). These results indicate that cytoprotective effect of compound 33 MP-Na is not different from that of its non-salt form.

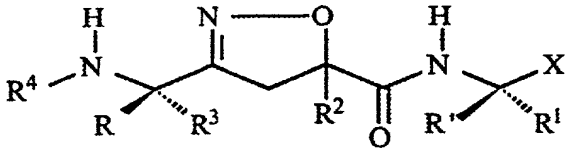
Therapeutic drugs are administrated after diagnosis of disease symptoms. We examined the protective effect of the compound of the invention on preinduced hepatocyte toxicity. Hepatocytes were treated first with TNF_α /ActD and then 100 μM of compound 33MP-Na was added at different time points. After 12 hrs of TNF_α /ActD treatment, cell viability was

determined by crystal violet staining. When added compound 33MP-Na between 0 and 6 hrs after TNF_{α} /ActD treatment, cell viability was not decreased (Fig. 16). Addition of compound 33MP-Na after 6 hrs of TNF_{α} /ActD treatment decreased cell viability in a time-dependent manner. No different results were obtained between compound 33MP-Na and Z-VAD-fmk. Treatment of mice with TNF_{α} /ActD induced high mortality (95%). This mortality was significantly reduced (~80%) when injected with compound 33MP-Na at 1 hr before, 0 h, or 2 hrs after TNF_{α} /ActD injection (Fig. 17). When administered 4 hrs after lethal challenge compound 33MP-Na still conferred a partial protection (50%). Moreover, death that occurs within 10-14 hrs in TNF α /ActD-injected animals was significantly delayed up to 24 hrs for the non-surviving compound 33MP-Na (data not shown).

The above results with inhibition of both anti-Fas antibody and TNF α -mediated hepatocyte apoptosis provide the strong evidence that a simple galenic formulation of caspase-inhibiting drugs constitutes a new promising therapeutic strategy for acute liver disease involving uncontrolled apoptosis. Both the compound of the invention and its salt form can also be used for promising therapeutic drugs for fulminant liver damage and mortality.

Claims

1. An isoxazoline derivative of the formula (I)



(I)

in which,

R and R' each independently represents hydrogen, simple alkyl chain (-SAC), simple cycloalkyl (-SCAC), aromatic (-Ar), or simple alkyl chain substituted with aromatic (-SAC-Ar);

R^1 represents -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC);

R^3 represents -SAC, -SCAC, -Ar, -SAC-Ar, or side chain of amino acids;

R^2 represents -H, -SAC, -SCAC, -Ar, or -SAC-Ar, or represents side chain of amino acids, or represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), or $-(CH_2)_nOC(=O)R^6$ (in which R^6 = -SAC, -SCAC, -Ar, or -SAC-Ar; and n=1 or 2);

R^4 represents

a) amino acid residue in which ① the carboxyl group attached to the chiral carbon of amino acid is bound to the amine group to form an amide bond, ② the chiral carbon of amino acid has either R or S configuration, ③ the amino group attached to the chiral carbon of amino acid is protected by formyl, acetyl, propyl, cyclopropylcarbonyl, butyl,

methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, butyloxycarbonyl, methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, butylcarbamoyl, dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, dibutylcarbamoyl or cyclopropylaminocarbonyl, or the amino group may be replaced with a hydrogen atom, and ④ the carboxyl group in the side chain may form an ester group with -SAC or -SCAC,

b) $-C(=O)R^7$ (in which R^7 = -SAC, -SCAC, -Ar, -SAC-Ar), $-CO_2R^8$ (in which R^8 = hydrogen or R^7), $-C(=O)NR^8R^8$, $-SOR^7$, $-SO_2R^7$, or -C(=O)CH=CH-Ar,

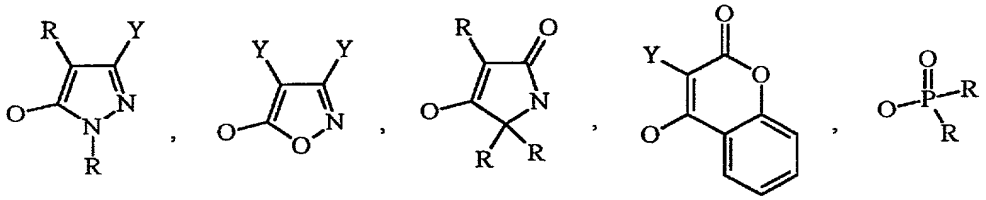
c) $-(C=O)-L-CO_2R^8$, in which L represents a divalent (=capable of double substitution) linker selected from a group consisting of C_{1-6} alkyl, C_{3-8} cycloalkyl, furan, thiophene, diazole (1,2 or 1,3), triazole (1,2,3 or 1,3,4), tetrazole, oxazole, isoxazole, thiazole, isothiazole, diazine (1,2 or 1,3 or 1,4), triazine, $-Ph(-R^9)-$ (in which R^9 = H, F, Cl, Br, I, CHO, OH, OCH_3, CF_3, OCF_3, CN, C(=O)Me), tetrahydrofuran, tetrahydrothiophene, 1,4-dioxane, $-CH=C(R^{10})-$ (in which R^{10}=H, methyl, ethyl), $-CH=CHCH(R^{10})-$, $-CH(OR^{10})CH_2-$, $-CH_2C(=O)CH_2-$, $-C(=O)CH_2CH_2-$

In cases where R^1 and the adjacent R', and/or R^3 and the adjacent R are connected to each other to form a cyclic compound, R^1-R' or R^3-R together represents $-(CH_2)_n-$, $-(CH_2)_n-O-(CH_2)_m-$, or $-(CH_2)_n-NR^{13}-(CH_2)_m-$ (in which $n+m<9$, R^{13}=-SAC, -SCAC, -Ar, -SAC-Ar, -C(=O)-SAC, -C(=O)-SCAC, -C(=O)-Ar, or -C(=O)-SAC-Ar);

X represents -CN, -CHO, $-C(=O)R^{14}$ (in which R^{14} = -SAC, -SCAC, -Ar, -SAC-Ar, or $-CHN_2$), $-C(=O)OR^{15}$ (in which R^{15} = -SAC, -SCAC, -Ar, or -SAC-Ar), $-CONR^{16}R^{17}$ (in which R^{16} and R^{17} each represents -H, -SAC, -O-SAC, -SCAC, -Ar, or -SAC-Ar), $-C(=O)CH_2O(C=O)Ar''$ (in which Ar''

= 2,6-disubstituted phenyl with F, Cl, Br, I, or CH_3), $-C(=O)CH_2OR^{18}$ (in which R^{18} represents -SAC, -SCAC, -Ar, or -SAC-Ar), or $-C(=O)CH_2OC(=O)R^{19}$ (in which R^{19} = -SAC, -SCAC, -Ar, or -SAC-Ar), or

X represents $-COCH_2$-W, wherein W represents $-N_2$, -F, -Cl, -Br, -I, $-NR^{20}R^{21}$ or $-SR^{22}$ (in which wherein R^{20}, R^{21} and R^{22} each independently represents -SAC, -SCAC, -Ar, or -SAC-Ar or R^{20} and R^{21} are connected to form a cyclic compound); or W represents



in which Y represents -OH, OR^{23} (in which R^{23} = -SAC, or -SCAC), $-C(=O)R^{24}$ (in which R^{24} = -H, -SAC, or -SCAC), -F, -Cl, -Br, -I, -CN, -NC, $-N_3$, $-CO_2H$, $-CF_3$, $-CO_2R^{25}$ (in which R^{25} = -SAC, or -SCAC), $-C(=O)NHR^{26}$ (in which R^{26} = -SAC, or -SCAC), and $-C(=O)NR^{27}R^{28}$ (in which R^{27}, R^{28} = -SAC, or -SCAC) and can be mono- or poly-substituted at its maximum regardless of the order and the kinds, the pharmaceutically acceptable salts, the esters and the stereochemically isomeric forms thereof.

2. The compound of formula (I) according to Claim 1, in which R^4 represents $-C(=O)(CH_2)_pCOOZ$ (in which p is 1 to 4, and Z is hydrogen, -SAC, -Ar or -SCAC).

3. The compound of formula (I) according to Claim 1, in which R^1 represents $-(CH_2)_nCOOZ$ (in which n is 1 or 2, and Z is hydrogen, -SAC, -Ar or -SCAC).

4. The compound of formula (I) according to Claim 1, in which

a) R and R' represent hydrogen,

b) R^1 represents $-CH_2COOH$, $-CH_2COOCH_3$, or $CH_2COOCH_2CH_3$,

c) R^2 represents $-(CH_2)_n(O)_mR^5$ (in which R^5 = -SAC, -SCAC, -Ar, -SAC-Ar; n=0, 1 or 2; and m=0 or 1), SAC, Ar, or Hydrogen,

d) R^3 represents $-CH(CH_3)_2$, $-CH_2COOH$, $-(CH_2)_2CO_2H$, $-CH_2C(O)NH_2$ or $-(CH_2)_2C(O)NH_2$,

e) R^4 represents $-C(=O)(O)_nR^{29}$ (in which n=0, 1; R^{29}= -Ar or -SAC-Ar), $-SO_2R^{30}$ (in which R^{30}= -Ar or -SAC-Ar), or $-C(=O)NHR^{31}$ (in which R^{31} = -Ar, or -SAC-Ar), or

f) X represents $-C(=O)CHN_2$, $-C(=O)CH_2Br$, $-C(=O)CH_2Cl$, $-C(=O)CH_2OPh$ or $-C(=O)CH_2OC(=O)Ar''$ (in which Ar"=2,6-dichlorophenyl, 2,6-difluoro-phenyl or 2,6-dimethylphenyl).

5. The compound of formula (I) according to Claim 1, which is selected from the group consisting of the following:

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-4-keto-pentanoic acid;

(2S)-2-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-5-phenoxy methyl-4,5-dihydro-isoxazole-5-carbonyl-amino}-succinic acid 1-(N-methyl-N-methoxy)-amide;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro -isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro -isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[(1S)-1-phenylmethyloxycarbonylamino-2-methyl-propyl]-4,5-dihydro

-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-1-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid(LP and MP);
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid(LP and MP);
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid(LP and MP);
(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[(1S)-1-(quinoline-2-yl-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;
(3S)-3-{3-[(1S)-1-(naphthalene-2-sulfonylamino)-2-methyl-propyl]-5-phenoxy-

methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-5-phenoxy-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[(1S)-1-(2S)-2-acetylamino-succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[(1S)-1-(naphthalene-2-carbonylamino)-2-methyl-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid (diasteromeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylethylcarbonylamino)-propyl]-5-phenyl-

methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenecarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-(1-naphtalenesulfonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid (diastereomeric mixture);

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)ethylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-((3-indolyl)methylcarbonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(cinnamoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethylsulfonylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-diazo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-bromo-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-2-yl-carbonylamino)-propyl]-5-(1-imidazolyl-methyl)-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(2-naphthalenecarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid;
(3S)-3-{3-[(1S)-1-(succinoylamino)-3-carboxy-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(1-naphthalenylcarbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(1-piperidinyl)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(isoquinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-4-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyl-oxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-difluorobenzoylo xy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-3-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoylo xy)- pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-phenyl-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dimethylbenzoylo xy)-pentanoic acid[diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(quinoline-8-carbonylamino)-propyl]-5-phenylmethy l-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(indole-2-carbonylamino)-propyl]-5-phenylmethyl-4, 5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(indole-3-carbonylamino)-propyl]-5-phenylmethyl-4, 5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(naphthalene-1-carbonylamino)-propyl]-5-methyl-4, 5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;

(3S)-3-{3-[2-methyl-(1S)-1-(benzofuran-2-carbonylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pen

tanoic acid;
(3S)-3-{3-[3-carboxy-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-piperidine)-pentanoic acid[diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(N-pyrrolidine)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-butyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2-naphthyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-propyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-phenoxy-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-hydroxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-phenylmethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-methoxymethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid [diastereomeric mixture];

(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-n-pentyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(succinoylamino)-propyl]-5-ethyl-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid;
(3S)-3-{3-[2-methyl-(1S)-1-(glutaroylamino)-propyl]-5-methyl-4,5-dihydro-iso-xazole-5-carbonylamino}-4-keto-5-(2,6-dichlorobenzoyloxy)-pentanoic acid; and
(3S)-3-{3-[2-methyl-(1S)-1-(phenylmethyloxycarbonylamino)-propyl]-4,5-dihydro-isoxazole-5-carbonylamino}-4-keto-pentanoic acid methyl ester.

6. A caspase inhibitor which comprises an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters or stereochemically isomeric forms thereof as claimed in any one of Claims 1 to 5.

7. A pharmaceutical composition for treating disease caused by inflammation or apoptosis which comprises as an active ingredient a therapeutically effective amount of an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, esters or stereochemically isomeric forms thereof as claimed in any of Claims 1 to 5 and pharmaceutically acceptable carrier.

8. The composition according to Claim 7, wherein the disease is selected from the group consisting of the diseases in which cells are abnormally died, dementia, cerebral stroke, brain impairment due to AIDS, diabetes, gastric ulcer, cerebral injure by hepatitis, fulminant hepatic failure (FHF), sepsis, organ transplantation rejection reaction, rheumatic arthritis, cardiac cell apoptosis due to ischemic cardiac diseases and anti-inflammation.

9. The composition according to Claim 7, wherein the disease is fulminant

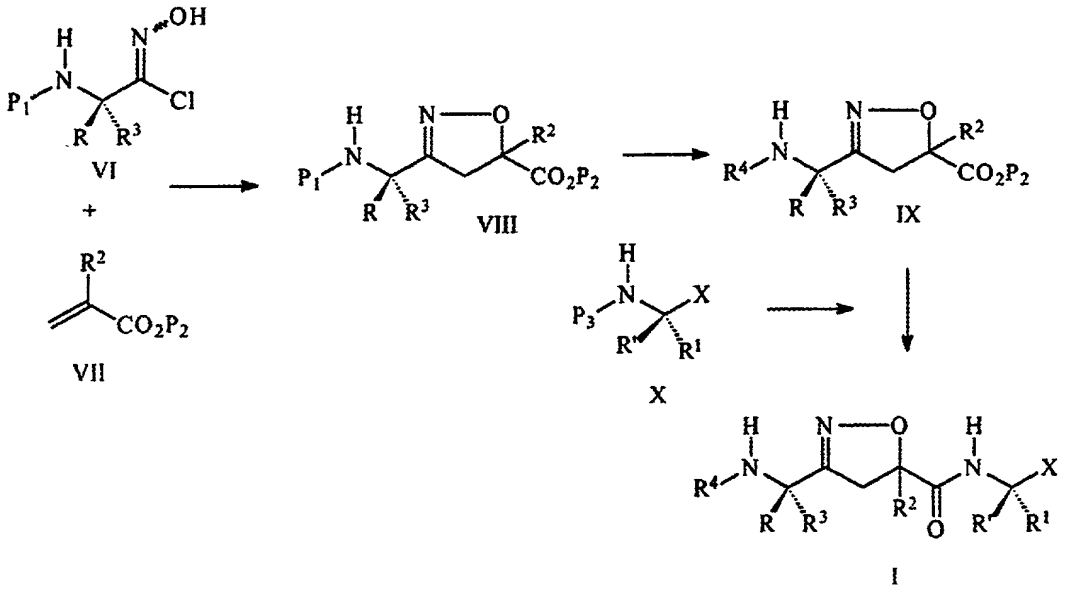
hepatic failure in human.

10. The composition according to Claim 7, in the form for administration orally, percutaneously, or by parenteral injection.

11. A method of treating patients suffering from the diseases caused by caspases activation, which comprises a local or systemic administration of a therapeutically effective amount of an isoxazoline derivative of the formula (I), the pharmaceutically acceptable salts, the esters or stereochemically isomeric forms thereof, according to any oen of Claims 1 to 5 or the pharmaceutical composition according to any one of Claims 7 to 10.

12. A process for preparing the pharmaceutical composition as claimed in any of Claims 7 to 10, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of formula (I) as claimed in any of Claims 1 to 5.

13. A process for preparing a derivative of the formula (I), the pharmaceutically acceptable salts, esters or stereochemically isomeric forms thereof, characterized in that hydroxamoyl chloride (VI) is reacted with acrylate derivative (VII) to give isoxazoline derivative (VIII), and isoxazoline derivative (VIII) is then deprotected and R^4 is introduced therein to give a compound of formula (IX) which is then reacted with a compound of formula (X) and, if necessary, the isoxazoline derivative (VIII) is directly reacted with the compound (X) to give a compound of formula (I), and if necessary, the compound of formula (I) having the protecting group P_1 is converted into other compound having substituent R^4.



in which the sustituents are the same as defined in Claim 1.

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1999/48608 4 November 1999 (04.11.1999) KR

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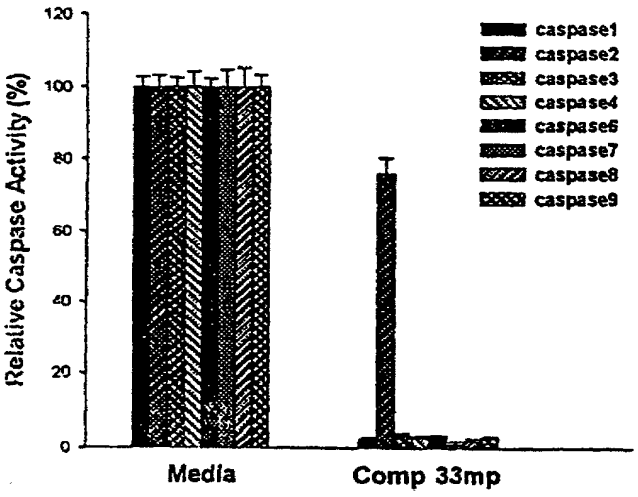
[Continued on next page]

(54) Title: CASPASE INHIBITOR



(57) Abstract: The present invention relates to an isoxazoline derivative of formula (I), the pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof, and the use of the derivative in inhibiting the activity of caspases. The present invention also relates to a pharmaceutical composition for preventing inflammation and apotosis which comprises the isoxazoline derivative, pharmaceutically acceptable salts, esters and stereochemically isomeric forms thereof and the process for preparing the same. The derivative according to the present invention can be effectively used in treating diseases due to caspases, such as, for example the disease in which cells are abnormally died, dementia, cerebral stroke, AIDS, diabetes, gastric ulcer, hepatic injure by hepatitis, sepsis, organ transplantation rejection reaction and anti-inflammation.

WO 01/21600 A1

FIG. 1

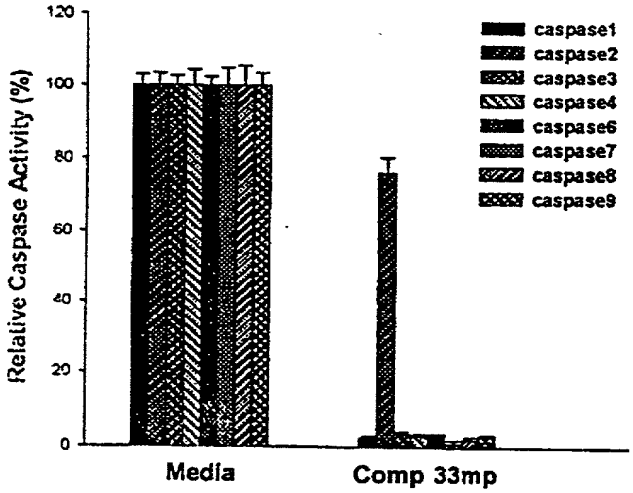

Relative Caspase Activity (%)
120
100
80
60
40
20
0
caspase1
caspase2
caspase3
caspase4
caspase6
caspase7
caspase8
caspase9
Media
Comp 33mp

FIG. 2

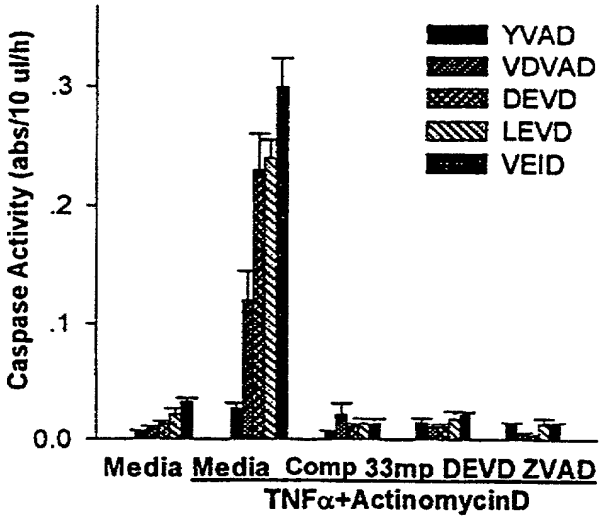

Caspase Activity (abs/10 ul/h)
.3
.2
.1
0.0
YVAD
VDVAD
DEVD
LEVD
VEID
Media Media Comp 33mp DEVD ZVAD
TNFα+ActinomycinD

FIG. 3

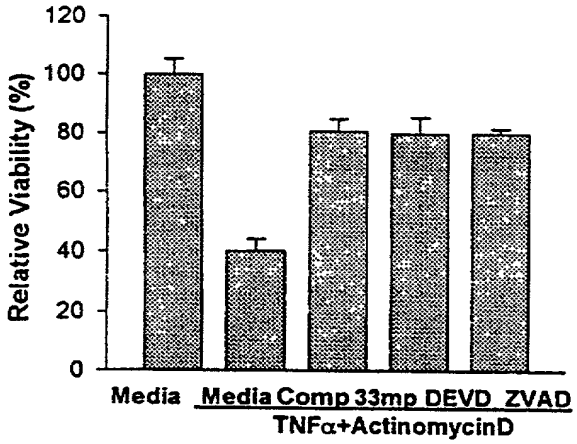

120
100
80
60
40
20
0
Relative Viability (%)
Media
Media
Comp 33mp
DEVD
ZVAD
TNFα+ActinomycinD

FIG. 4

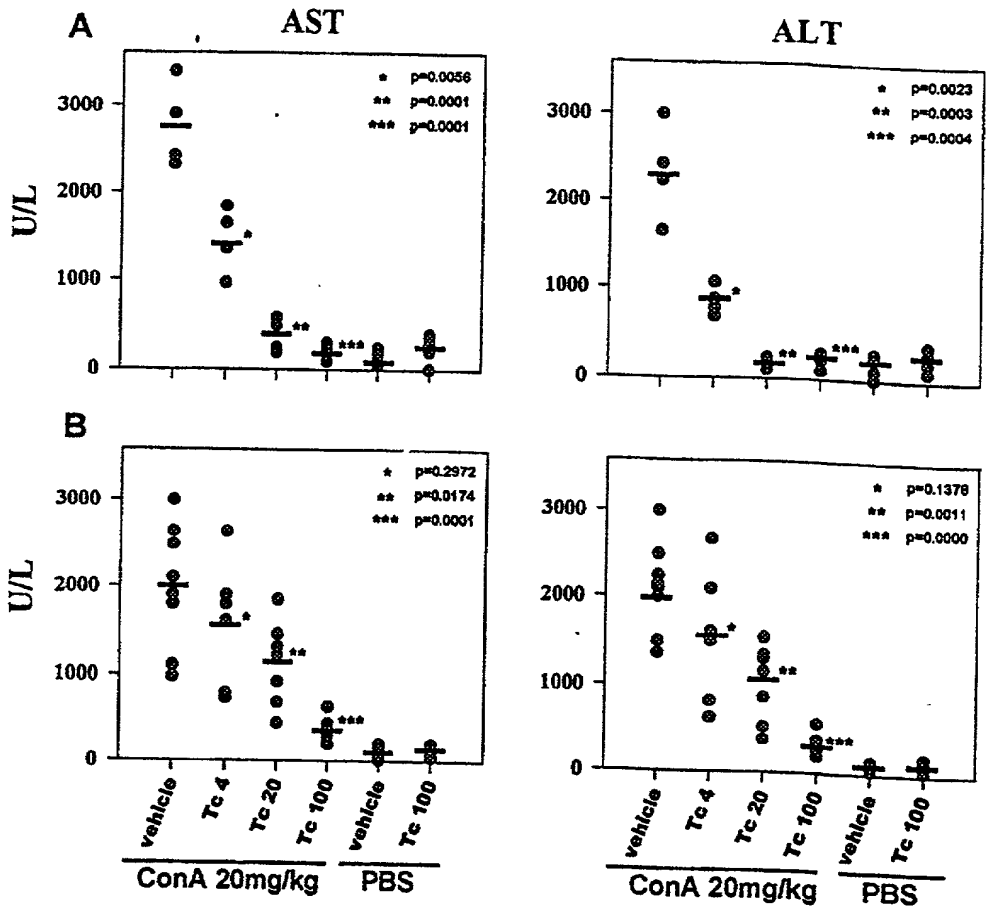

A
AST
ALT
B
U/L
3000
2000
1000
0
* p=0.0056
** p=0.0001
*** p=0.0001
* p=0.0023
** p=0.0003
*** p=0.0004
* p=0.2972
** p=0.0174
*** p=0.0001
* p=0.1378
** p=0.0011
*** p=0.0000
vehicle
Tc 4
Tc 20
Tc 100
vehicle
Tc 100
ConA 20mg/kg
PBS

FIG. 5

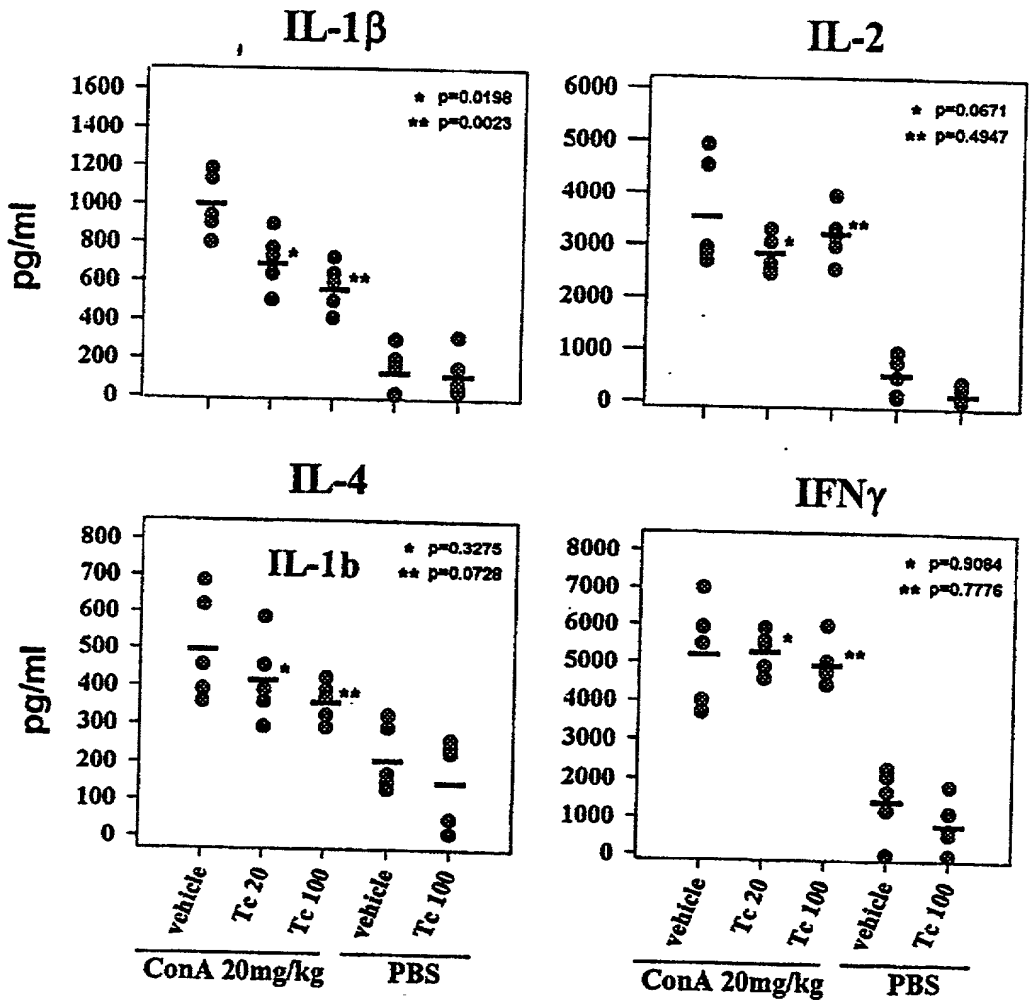

IL-1β
pg/ml
1600
1400
1200
1000
800
600
400
200
0
* p=0.0198
** p=0.0023
IL-2
6000
5000
4000
3000
2000
1000
0
* p=0.0671
** p=0.4947
IL-4
IL-1b
800
700
600
500
400
300
200
100
0
* p=0.3275
** p=0.0728
IFNγ
8000
7000
6000
5000
4000
3000
2000
1000
0
* p=0.9084
** p=0.7776
vehicle
Tc 20
Tc 100
vehicle
Tc 100
ConA 20mg/kg
PBS

FIG. 6a

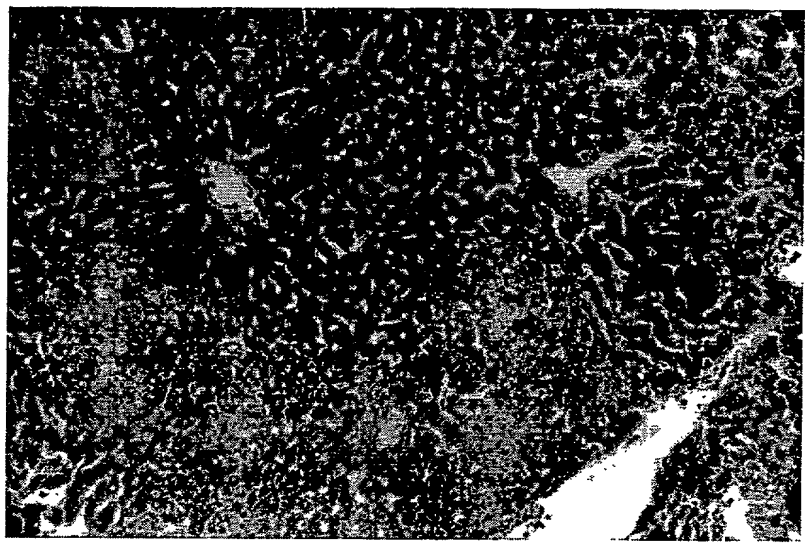


FIG. 6b

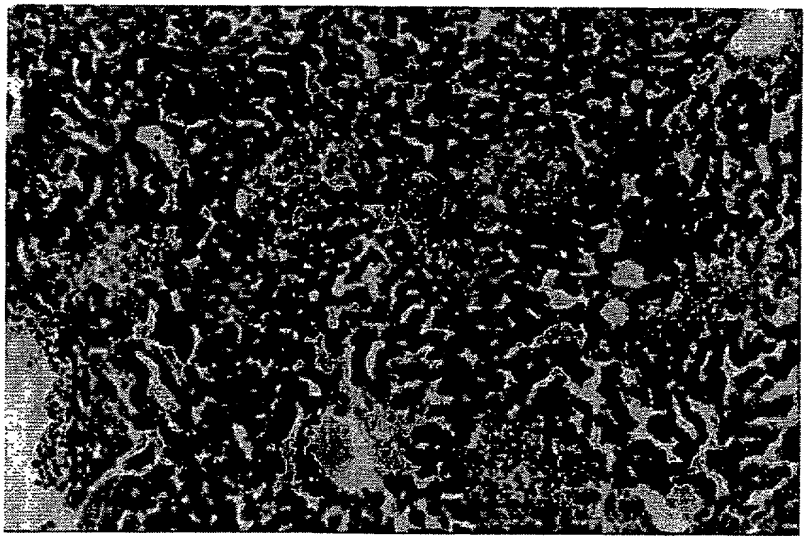


FIG. 6c

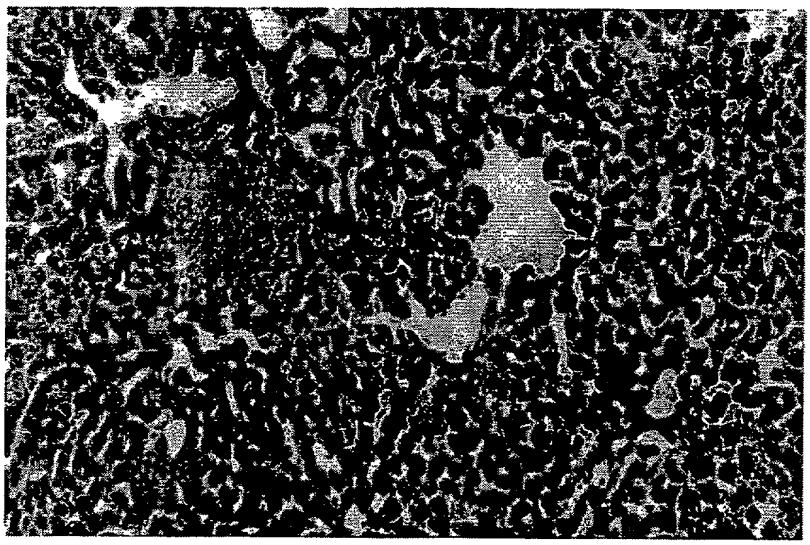


FIG. 6d

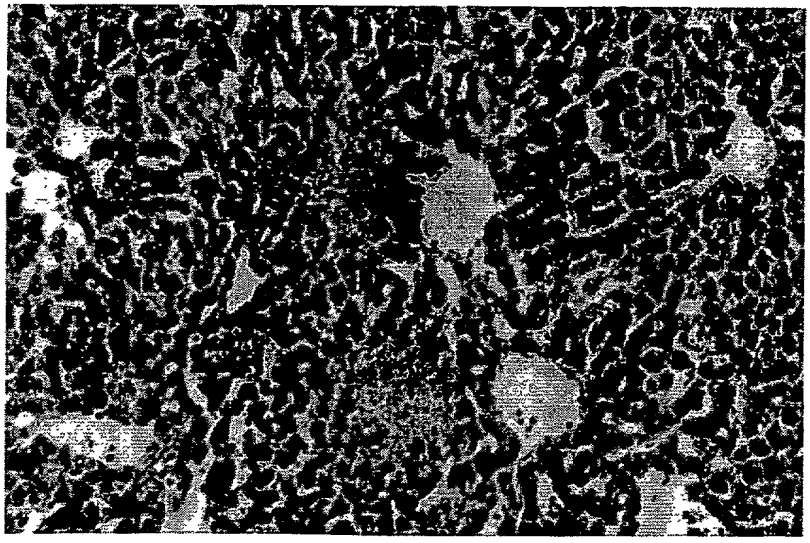


FIG. 6e

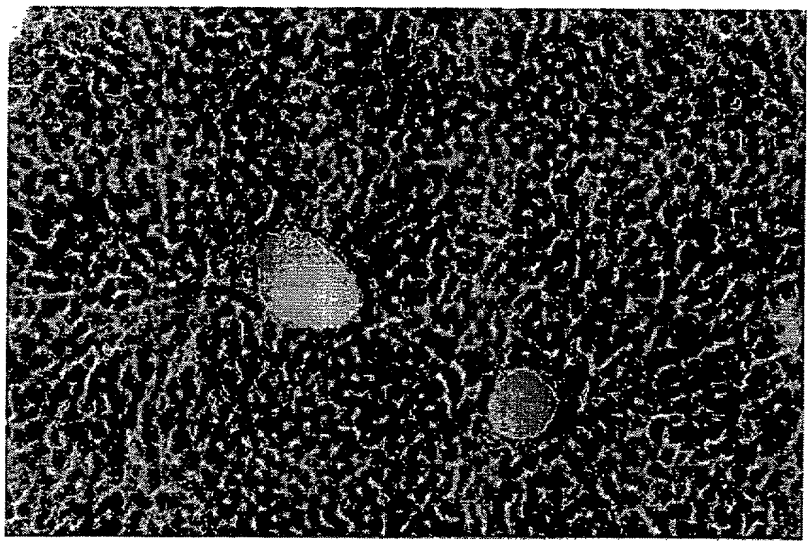


FIG. 6f

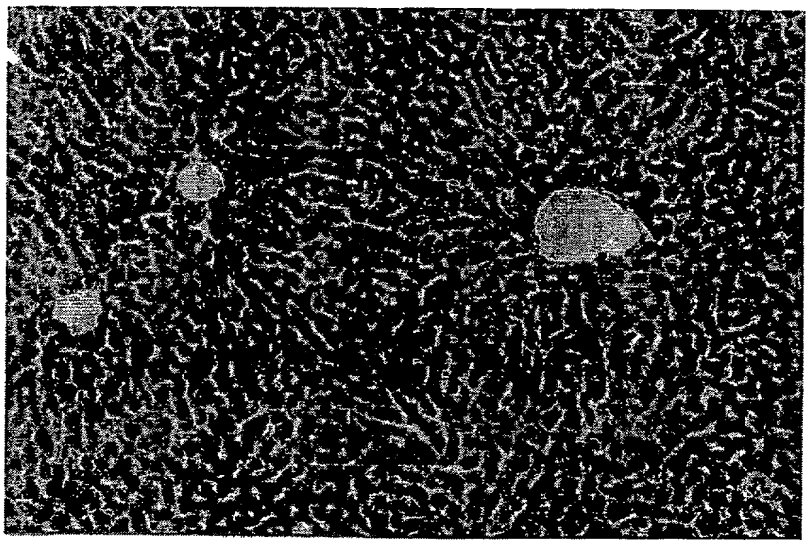


FIG. 6g

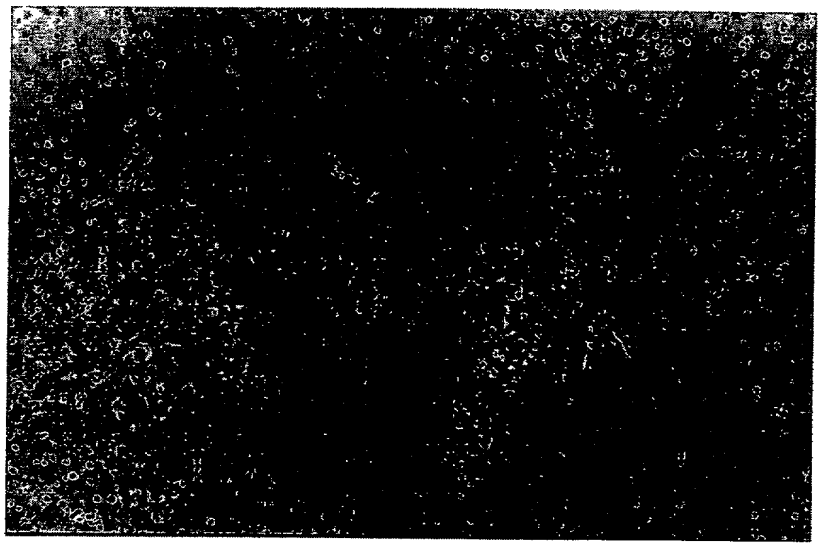


FIG. 6h

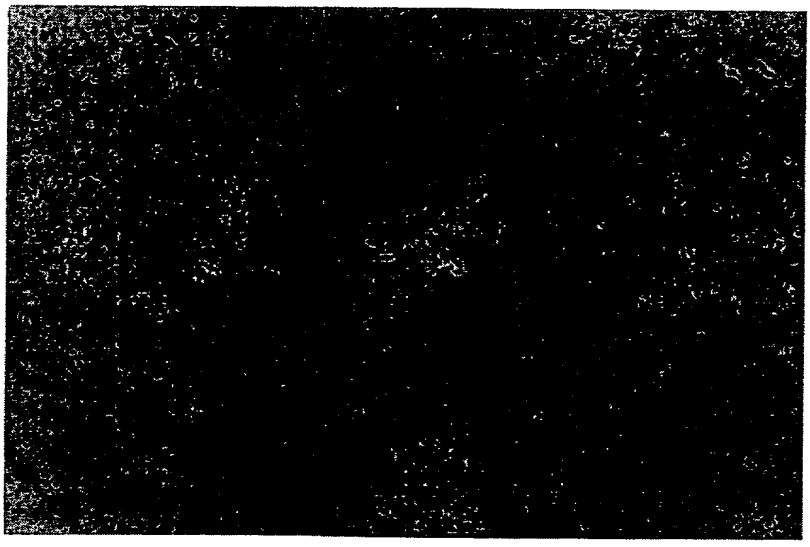


FIG. 6i

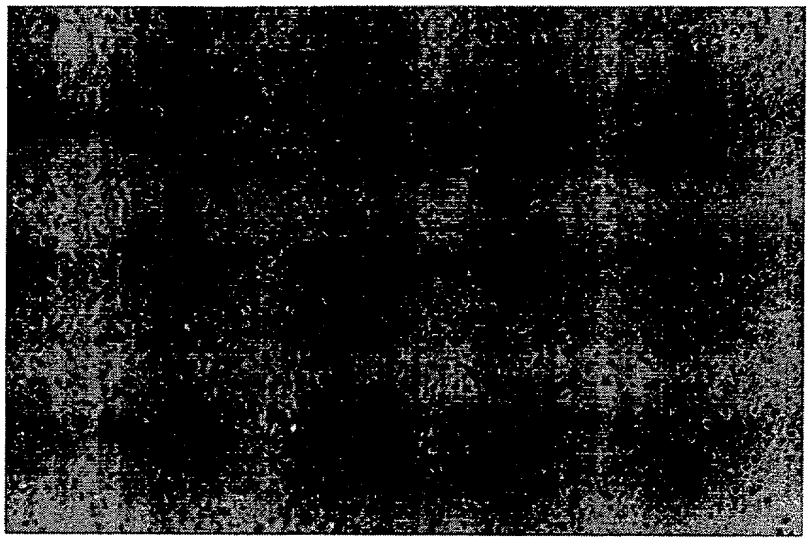


FIG. 6j

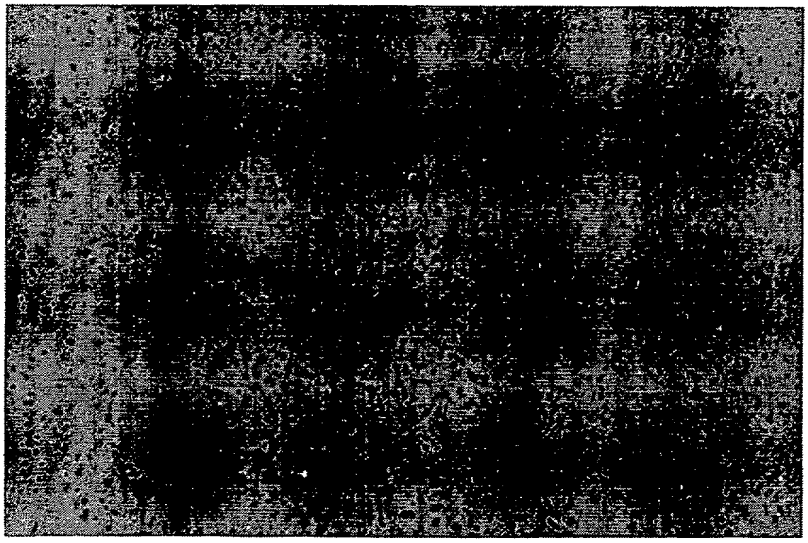


FIG. 6k

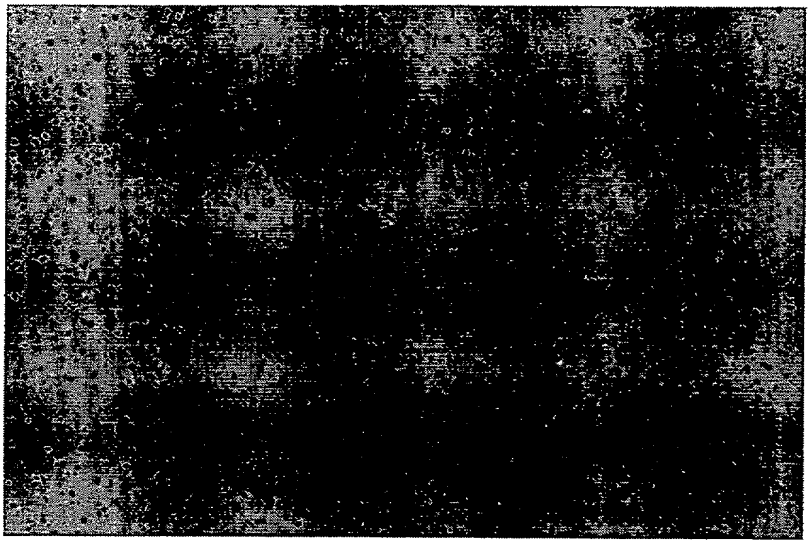


FIG. 6l

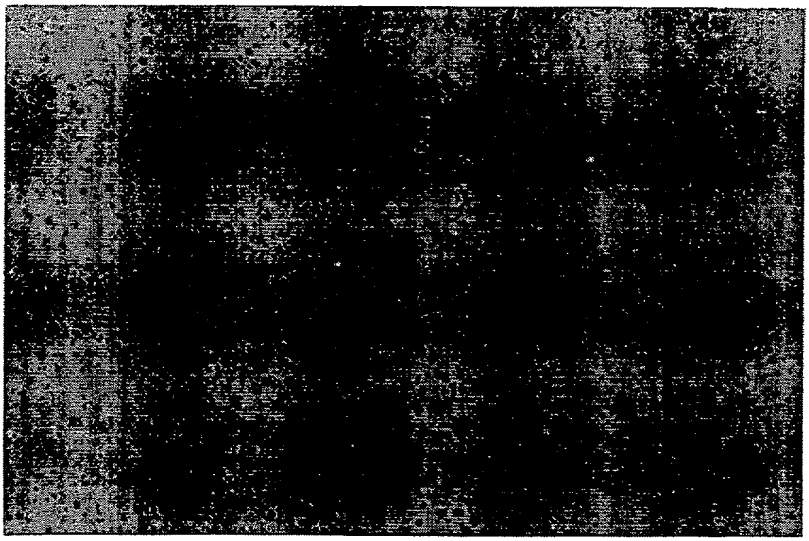


FIG. 7

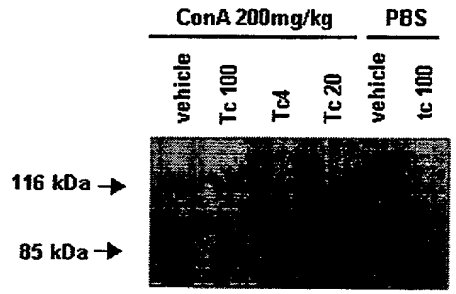

ConA 200mg/kg
PBS
vehicle
Tc 100
Tc4
Tc 20
vehicle
tc 100
116 kDa
85 kDa

FIG. 8

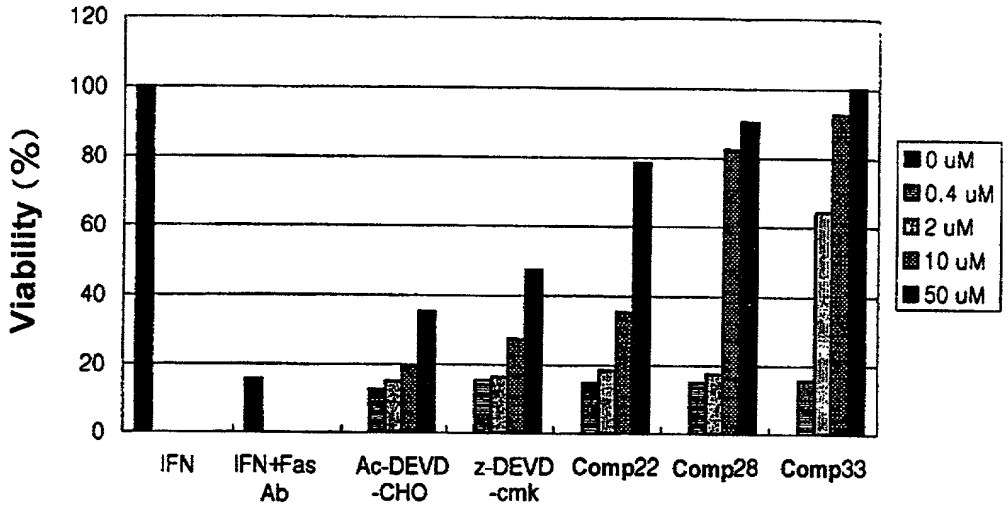

Viability (%)
120
100
80
60
40
20
0
IFN
IFN+Fas Ab
Ac-DEVD -CHO
z-DEVD -cmk
Comp22
Comp28
Comp33
0 uM
0.4 uM
2 uM
10 uM
50 uM

FIG. 9

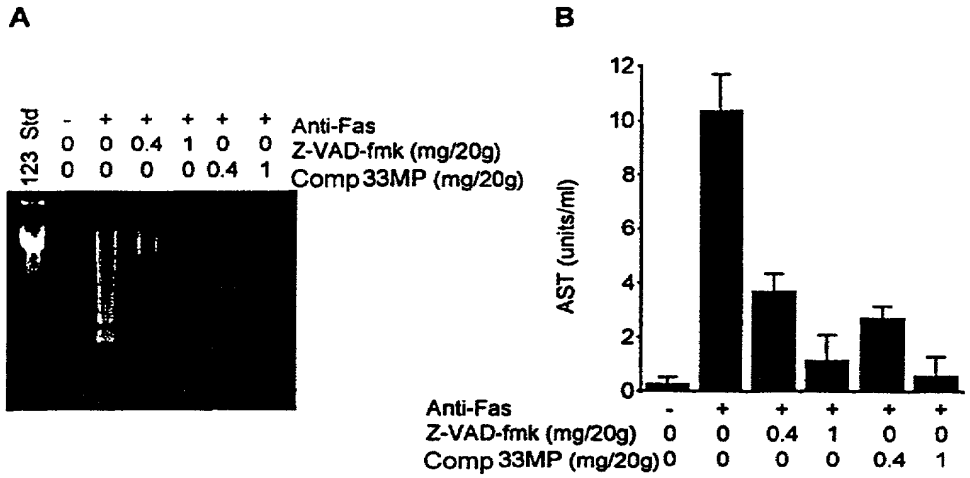

A
B
123 Std
Anti-Fas
Z-VAD-fmk (mg/20g)
Comp 33MP (mg/20g)
AST (units/ml)
0
2
4
6
8
10
12

FIG. 10

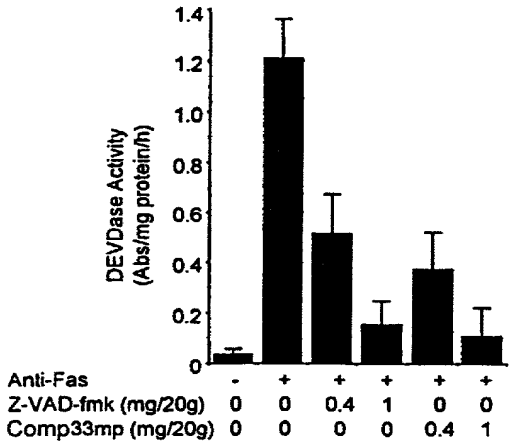

DEVDase Activity
(Abs/mg protein/h)
0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
Anti-Fas
Z-VAD-fmk (mg/20g)
Comp33mp (mg/20g)

FIG. 11

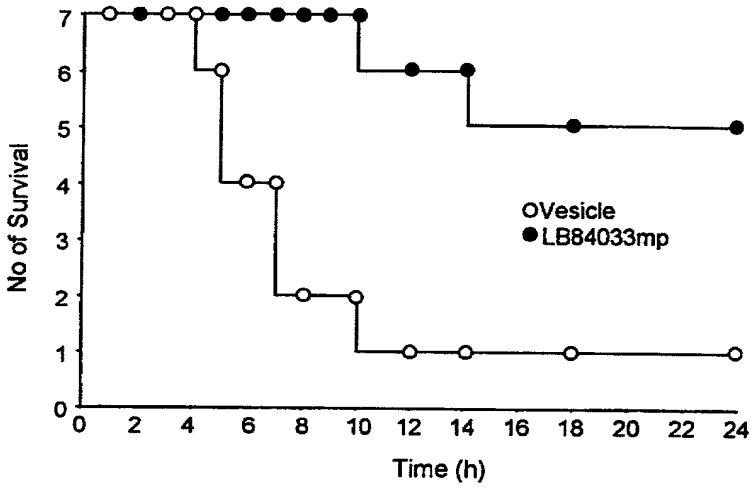

No of Survival
Time (h)
OVesicle
●LB84033mp

FIG. 12

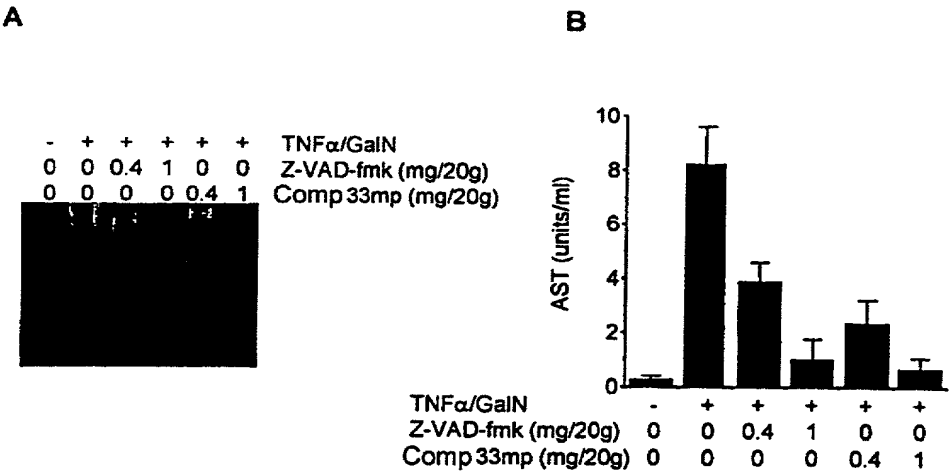

A
B
TNFα/GalN
Z-VAD-fmk (mg/20g)
Comp 33mp (mg/20g)
AST (units/ml)

FIG. 13

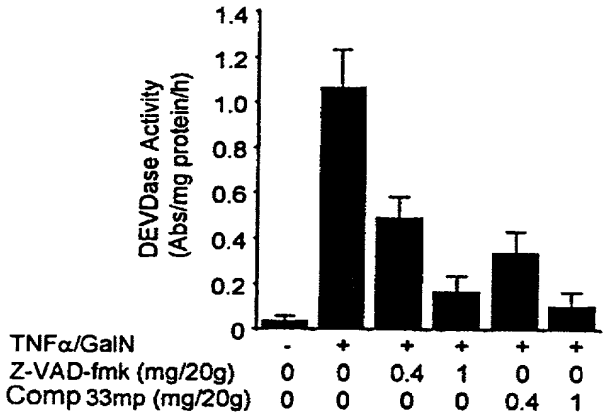

DEVDase Activity (Abs/mg protein/h)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
TNFα/GalN - + + + + +
Z-VAD-fmk (mg/20g) 0 0 0.4 1 0 0
Comp 33mp (mg/20g) 0 0 0 0 0.4 1

FIG. 14

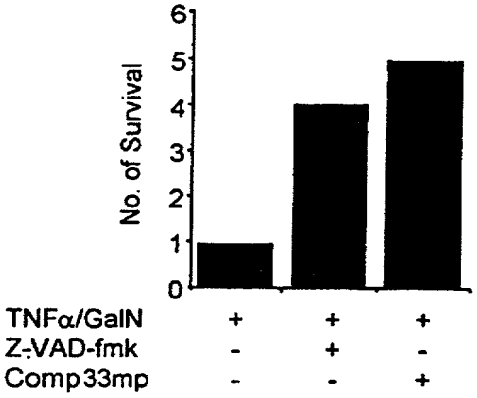

No. of Survival
6
5
4
3
2
1
0
TNFα/GalN + + +
Z-VAD-fmk - + -
Comp33mp - - +

FIG. 15

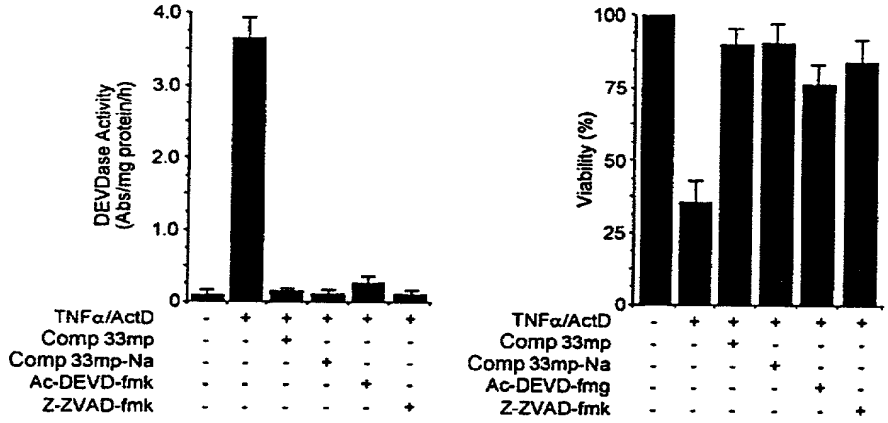

DEVDase Activity (Abs/mg protein/h)
4.0
3.0
2.0
1.0
0
TNFα/ActD - + + + + +
Comp 33mp - - + - - -
Comp 33mp-Na - - - + - -
Ac-DEVD-fmk - - - - + -
Z-ZVAD-fmk - - - - - +
Viability (%)
100
75
50
25
0
TNFα/ActD - + + + + +
Comp 33mp - - + - - -
Comp 33mp-Na - - - + - -
Ac-DEVD-fmg - - - - + -
Z-ZVAD-fmk - - - - - +

FIG. 16

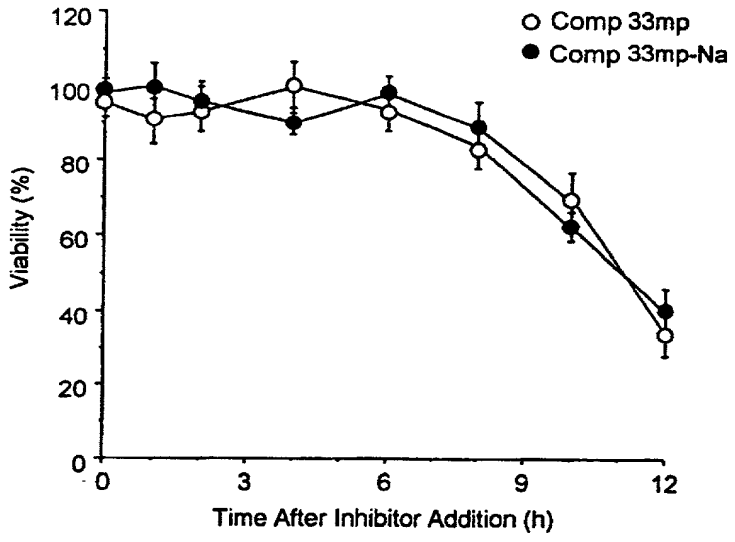
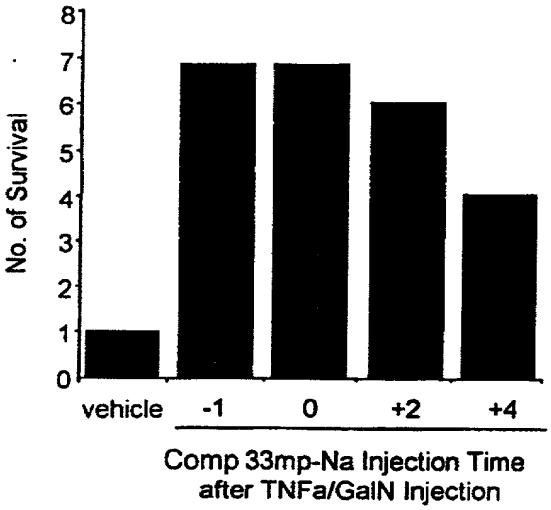

Comp 33mp
Comp 33mp-Na
Viability (%)
120
100
80
60
40
20
0
0
3
6
9
12
Time After Inhibitor Addition (h)

FIG. 17


No. of Survival
0
1
2
3
4
5
6
7
8
vehicle
-1
0
+2
+4
Comp 33mp-Na Injection Time
after TNFa/GalN Injection

Declaration and Power of Attorney For Patent Application
English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and join inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

PROCESS FOR PREPARING A 1-SUBSTITUTED 5-HYDROXYMETHYL IMIDAZOLE

the specification of which

(check one)

[ ] corresponds to _____ , filed on _____

[x] was filed on September 18, 2000 as United States Application No. or PCT Application Number PCT/KR00/01047 and was amended on _____

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined In Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

			Priority Not Claimed
PCT/KR99/00561 (Number)	KR (Country)	17/09/1999 (Day/Month/Year Filed)	[ ]
1999-48608 (Number)	KR (Country)	04/11/1999 (Day/Month/Year Filed)	[ ]

(Number)	(Country)	(Day/Month/Year Filed)	[ ]

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of the United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (Patented, pending, abandoned)
PCT/KR00/01047	September 18, 2000	Pending
(Application Serial No.)	(Filing Date)	(Status) (Patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (Patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section

1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (*list name and registration number*)

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